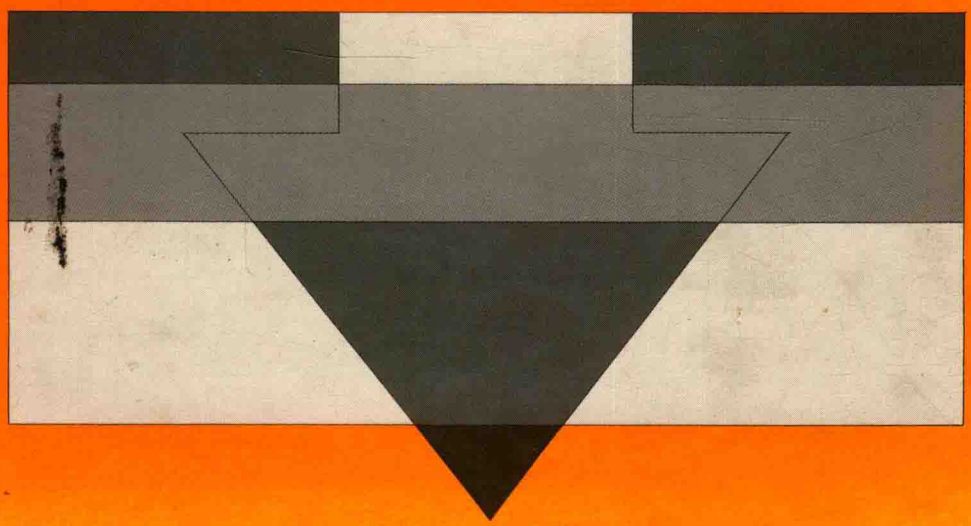
CANCER CAUSING CHEMICALS

N. IRVING SAX



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Assisted by:

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KEY TO ABBREVIATIONS

bdw - wild bird species
brd - bird (domestic or lab)
CAR - carcinogenic effects
cat - cat
chd - child
ckn - chicken
ctl - cattle
dck - duck
dog - dog
dom - domestic
EPA - Environmental Protection Agency
ETA - equivocal tumorigenic agent
eye - administration into eye (irritant)
frg - frog
g or gm - gram
gpg - guinea pig
grb - gerbil
ham - hamster
hmn - human
ial - intraaural
IARC - International Agency for Research on Cancer
iat - intraarterial
ice - intracerebral
icv - intracervical
idr - intradermal
idu - intraduodenal
ihl - inhalation
imm - immersion
imp - implant
ims - intramuscular
inf - infant
ipc - intraplacental
ipl - intrapleural
ipr - intraperitoneal
irn - intrarenal
isp - intraspinal
itr - intratracheal
ivg - intravaginal
ivn - intravenous
LC50 - lethal concentration 50 percent kill
LCLo - lowest published lethal concentration
LD50 - lethal dose 50 percent kill
mam - mammal (species unspecified)
man - man
mg - milligram (one thousandth of a gram;10^{-3} gram)
mky - monkey
mul - multiple routes
mus - mouse
MUT - in vivo mutagenic effects
NEO - neoplastic effects
ocu - ocular
open - open irritation test
orl - oral
OSHA - Occupational Safety and Health Administration
par - parenteral
pgn - pigeon
pig - pig
qal - quail
rat - rat
rbt - rabbit
rec - rectal
scu - subcutaneous
sql - squirrel
TER - teratogenic effects
trk - turkey
ug - microgram (one millionth of a gram;10^{-6} gram)
unk - unreported
UNS - toxic effects unspecified in source
wmn - woman

This book is respectfully dedicated to:

DOCTOR WILHELM CARL HEINRICH HUEPER

whose lifelong struggle and scientific contributions in environmental cancer prevention are an inspiration to us all.

Preface

The complexities of our times are such that anyone who wants to avoid cancer-causing exposure must either learn more about our science and technology or live in a state of constant anxiety or resignation. Just as prehistoric man feared the awesome forces of the natural world, people in industrialized nations live in fear of the unnatural world we have created. It is tempting to resign ourselves to the fact that we live in a sea of carcinogens, and there is no way to part that sea.

Cancer Causing Chemicals is particularly intended for the people who haven't yet thrown up their hands in despair, and hopefully never will.

Remember, some cancer can be prevented and the means for prevention is at hand. As an oversimplication, we might reduce environmental exposure to two classes: voluntary and involuntary. Cigarette smoking is known to be very harmful, and most people who smoke know that. Though it is an addictive habit, it has to be considered voluntary. Air pollution, on the other hand, whether from cigarette smoke or factories, is an involuntary exposure. It is possible to avoid drinking polluted water, but one cannot avoid breathing the air. You can avoid a hazardous job, install a carbon filter for your tap water, grow your own organic food, and avoid consumer products labeled as containing hazardous chemicals.

Most of the conditions come under the heading of involuntary exposure. If you are exposed to carcinogens because the contents of a product have not been labeled properly, this falls under involuntary exposure. Many products are formulated to give the best eye appeal and most advantageous physical properties for their intended use and many contain carcinogens that are not necessary. The most one usually finds in the way of a warning is a label listing the contents of the package.

It is intended here to present the information necessary for people to avoid some of the hazards not yet covered by law.

Our government, for a host of reasons, can do no more than order removal of the most glaring cancer hazards from our environment. We get to choose among the rest, and the more you know about the hazards involved, the safer you are.

Just as important as individual protection is the collective response of an informed public. As more people become aware of the serious and needless hazards in our environment, pressure increases for our elected officials and government agencies to take stronger positions. In this way, the expertise of specialists both in government and industry can be combined to take preventive steps before a catastrophe strikes.

N. Irving Sax

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I wish to acknowledge the vital assistance and guidance of Richard J. Lewis, Sr., Editor of the Registry of Toxic Effects of Chemical Substances, NIOSH, DHSS, PHS, CDC.

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Last, but far from least, the professional assistance of Alberta Gordon, Managing Editor of Van Nostrand Reinhold Company, in setting up the format and presentation of this book.

How to Use This Book

Cancer Causing Chemicals is divided into two sections.

Section I includes Chapters 1 through 4 and Section 2 includes Chapters 5 and 6. In this way we have separated our theoretical and philosophical material from our tabular and numerical data.

To review the Contents:

1. "Chemical Carcinogenesis and Its Relevance for the General Population," is written by Elizabeth K. Weisburger, Ph.D.
2. "Carcinogens in the Workplace," is by David Schottenfeld, M.D., and Joanna Haas, M.D.
3. "Control of Workplace Carcinogens," is by Benjamin Feiner, P.E.
4. This is a chapter on the regulations which affect our use of carcinogens, how these work in practice and some insight into how big business handles the problem of carcinogens. Some remedies are suggested by Barry I. Castleman.

Chapter 5, in Section 2, lists nearly 25,000 synonyms and cross references to each of the 2400 basic carcinogens which are listed, described, and discussed in Chapter 6.

Chapter 6 rates the carcinogenicity of each of the 2400 entries as "conclusive," "suggestive," or "indeterminate," based upon an exhaustive literature search against criteria applied to this mass of data by means of a computer. Also listed are any IARC findings about each entry.

Each carcinogen contains a NIOSH number for purposes of identification from an average of seven synonyms for each entry. There is also included a CAS number for each of the 2400 entries so that the reader who wishes to continue his research, can do so by keying the CAS number into the enormous files of the ACS, as well as to the memories of giant computers located throughout the country. For instance, by use of the CAS number, we have often entered the 12+ memory banks of the Interactive Science Corporation, CIS of Washington, D.C. computer.

We have obtained NIOSH printouts on the toxic effects of chemical substances giving far more advanced information than anything published.

The appendix lists all of the references directly associated with Chapters 5 and 6. Furthermore, Chapters 1, 2, and 3 list hundreds of references immediately following the text. Chapter 4 lists references along with the text.

We have gone to considerable effort in compiling this book to make the list of carcinogens complete. The list is as complete as can be found anywhere. Thus, if the material you are interested in is not listed in either Chapter 5 or 6, it is probably not known as a carcinogen. If, on the other hand it is listed, you can read about it, and if further information is necessary, you can study the pertinent references.

CONTENTS

Section I

1

Chemical Carcinogenesis And Its Relevance For The General Population

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One may get the impression from various news sources that there is a tremendous increase in cancer incidence. There have been increases in certain types of cancer, but the death rates from diseases such as tuberculosis, diphtheria or pneumonia have gone down. Furthermore, the occurrence of some types of cancer is decreasing; stomach cancer in particular is decreasing.[1,2] Often overlooked is the fact that bone tumors have been discovered in fossils of dinosaurs or cave bears, creatures which existed long before the development of technology. Even ancient man was not free of cancer. Mummies from Egypt have shown the presence of bone tumors and cancer of the nasopharyngeal area, a type still common in East Africa. Mummies from Peru have shown both bone tumors and melanoma which had spread or metastasized to the bones. Egyptian papyruses and the writings of respected physicians such as Hippocrates or Galen from centuries past all mentioned diseases now recognized as different forms of cancer.[3]

Although cancer has been known for thousands of years, it is only within the past century that epidemiologists, by studying occupational and other exposed groups, have been able to pinpoint certain chemical compounds responsible for initiating this disease in man. The International Agency for Research on Cancer (IARC) considers that the compounds or processes listed in Table 1.1 are associated with cancer in humans.[4] The list includes drugs and a natural product, but the greater proportion of these compounds is found in chemical, metal refining, polymer, and allied industries. Although most of these compounds were once encountered in occupational situations, some are no longer used commerically; those that are used have fairly severe regulations on exposure.

Within the past decade several occupational health acts have given various regulatory agencies broad powers to regulate the presence of carcinogens in the workplace, and to ban their use entirely if it seems warranted. Under such authority, the exposure limits for several high volume industrial intermediates, vinyl chloride for example, have been set at 1 ppm. Other substances, including benzidine-based dyes and the nematocide 1,2-dibromo-3-chloropropane, are so severely regulated that their commercial production and use will probably disappear.

Despite these regulatory measures, the rate of certain types of cancer continues to increase. Since most of the population is not involved in the production of chemicals, other possible carcinogens may be affecting the general population. It is highly probable that no single potent carcinogen is involved but that combinations of several factors, each with a weak effect, may be responsible. Some of these factors, as well as their possible synergistic action, will be discussed. Also, because the infectious diseases are no longer the most common causes of death, the probability of developing cancer increases. As more is learned about carcinogenic factors in the environment, it is now realized that other factors besides industrial activity are probably responsible for much of the general cancer incidence.

Smoking

Probably one of the most important causes of cancer in the general population, smoking increases lung, buccal cavity, pharnyx, pancreas and bladder cancer.[5-7] This is a dangerous habit because of the presence of many toxic and carcinogenic substances in tobacco smoke. The gaseous phase of tobacco smoke usually contains carbon monoxide, ammonia, hydrazine, vinyl chloride, nitrosamines, aldehydes, and other substances.[8]

The particulate phase contains numerous polycyclic aromatic hydrocarbons, many of which are known carcinogens when tested singly. Aromatic amines, including the human bladder carcinogen 2-naphthylamine, have also been identified; they are probably the results of pyrolysis processes. In addition, several fairly potent nitrosamines have been found

in tobacco smoke and in unburned tobacco.[9] Structurally these are derived from nicotine or its degradation products. The possible additive or synergistic effects of the carcinogens in tobacco smoke should be considered in evaluating the final result.

Smoking increases the risk of cancer from other types of exposures; smokers who also are exposed to asbestos have up to a 90-fold greater risk of developing lung cancer than the general population.[10,11] Likewise, uranium miners who smoke increase the cancer risk above their usual rate, which is already higher than that of the general population.[12]

Smoking along with excessive consumption of alcohol leads to cancer of the mouth, pharynx, esophagus, and liver.[13] Traces of nitrosamines known to be carcinogenic in animals have been detected in many brands of beer, especially those that used malt which was gas-fired during drying.[14] Changing the technique for drying the malt may lower or eliminate these hazardous nitroso constituents. Nitrosamines were not detected in wines or distilled spirits, but there are some reports that the congeners present in brandies and similar beverages had a carcinogenic effect in rats.[13,15,16] Thus, the increased cancer rate in people using both alcoholic beverages and tobacco to excess may be explained because of either a promoting effect of alcohol or because of the presence of traces of known carcinogens.

Radiation

Another factor affecting the entire population is exposure to various types of low-level radiation, including sunlight, cosmic radiation, and x-rays received during medical and dental treatment.

Excessive exposure to sunlight, in accordance with the fad for excessive sunbathing, eventually leads to increased risk of skin cancer; light-skinned people run an even greater risk.[17] There is also the possibility of an increased melanoma occurrence.[18] The dichotomy is that some sunlight is necessary for formation of vitamin D to prevent rickets and similar conditions.

Radiation also includes background cosmic radiation and naturally occurring radiation in soil and rocks.[19,20] Living at high altitudes such as Denver, Bogata, and Nepal, and flying at high altitudes, increases the risk from cosmic radiation. On the other hand, uranium mining causes a higher incidence of neoplasms because the uranium and radium in the mines decompose to radon gas and other products. These radioactive gases are thought to be responsible for the exposure in uranium mines. Other types of mines, as well as buildings located over mine tailings or buildings made with stones carrying traces of radioactive material, may also contain radon.

Repeated exposure to radiation, even at levels that were once considered reasonable, has led to an increase of certain types of cancer.[19] One study, which monitored women who were fluoroscoped repeatedly for one year or longer as part of a medical treatment for tuberculosis, showed that the occurrence of breast cancer increased.[21,22] Since more than 40% of radiation exposure results from medical or dental x-rays, usually for diagnostic purposes, it has been suggested that this source of radiation exposure be reduced to the minimum required.[23]

Location or Geographic Location

The *Atlas of Cancer Mortality for US Counties* reveals wide variations in geographic patterns for different types of cancer.[24,25] Certain areas have much higher rates than usual, sometimes but not always coinciding with the location of chemical industry.[26,27] For example, there is a high rate of lymphoma and similar diseases in residents of the industrialized-urbanized New Jersey-New York-Philadelphia area.[28] However, there are discrepancies in attempting to correlate the location of industry with all types of cancer. For example, the cancer incidence in the industrialized New Jersey-New York-Philadelphia metropolitan region and that for the rest of the United States are tending to converge.[29] As industrial pollution and exposure are controlled through regulation, the influences which affect nonindustrial areas may play a larger role.

However, there are isolated but discrete regions in rural areas where cancer rates are high. The elevated leukemia risk in certain farming regions of Nebraska was correlated with heavy production of corn and, presumably, exposure to pesticides and similar agricultural chemicals.[30] This type of exposure could not explain why Amish males living in rural areas of Indiana, Ohio and Pennsylvania had higher occurrences of leukemia and lymphoma than did non-Amish of the same counties.[31] Breast and stomach cancer rates were higher in Amish women than in non-Amish women; conversely, some types of cancer were less frequent in the Amish. A possible genetic effect may be involved. Similarly, in male Acadians living in rural nonindustrial areas of Louisiana, the incidence of cancer of the mouth, tongue, larynx, bladder, and various other organs was higher than that for the overall United States.[32] Although some kinds of cancer in women were higher than normal for the South, others were much lower than expected. In the case of the Acadians, it was indicated that a genetic effect ("founder effect") plus considerable inbreeding may have caused the higher than usual cancer rate.[32]

The similarity of cancer rates between industrial and nonindustrial areas has been also discussed by Higginson and Muir.[33] As an example, the cancer incidence in the nonindustrial but commercial city of Geneva, Switzerland, is like that in urban areas of England where there is significant industrial development.

Drug Use

The continual use of certain drugs is associated with increases in some types of cancer, a factor which should be considered

by physicians recommending treatment with any such drug. A careful risk-benefit assessment is needed to insure that the benefit to the patient outweighs any risk from a drug.

Most important among these drugs are the cytotoxic agents generally employed for treating neoplastic diseases. The earliest carcinogenic effect noted from cytotoxic drugs was in patients receiving chlornaphazine for Hodgkin's disease or polycythemia vera. After relatively high doses over a few years, most of these patients developed the type of bladder cancer found in industrial workers exposed to the parent compound 2-naphthylamine. The clinical use of chlornaphazine has been discontinued. Drugs currently used include melphalan for treatment of multiple myeloma, but this may cause acute leukemia later. Cyclophosphamide, used to treat both neoplastic or autoimmune diseases, has also increased the risk of acute leukemia. Treatment with procarbazine is also associated with an increased possibility of developing other types of cancer; thiotepa is under suspicion for similar reasons.[4,34-36] Although animal tests on methotrexate have been negative, there are several case reports indicating that continued treatment with this drug is not without risk.[37,38] Radioisotopes used in various diagnostic procedures or treatments, ^{32}P, radium, and Thorotrast, for example, are correlated with neoplasms occurring many years later. Use of Thorotrast as a diagnostic agent was particularly hazardous because it remained in such organs as the spleen, liver, etc., due to negligible clearance by the body, and sarcomas often arose many years later.[36]

Immunosuppressive drugs including antimetabolites, corticosteroids, and antilymphocyte serum employed during renal transplants also contribute to an increased risk of cancer.[35] The specific tumors involved were lymphomas, skin cancer, hepatobiliary cancers, soft tissue sarcomas, and possibly adenocarcinomas of the lung. Overall, the risk varied from 2.5 times expected (for hepatobiliary cancer and soft tissue sarcomas) to 20–35 times (for lymphomas), or to as much as 150–350 times expected (for reticulum cell sarcomas).[36,39] In another study it was evident that kidney transplant patients treated with the immunosuppressive drugs azathioprine, cyclophosphamide, or chlorambucil had a 60-fold increase of lymphomas, an excess of skin cancer, and more mesenchymal tumors than expected.[35] Patients treated with these drugs for rheumatoid arthritis, glomerulonephritis, or dermatomyositis also had an excess of the same tumors, but to a lesser extent.[35]

The androgenic–anabolic steroids methyltestosterone, testosterone, and oxymetholone have been part of the treatment for aplastic and other anemias. These steroids have also been taken by athletes to increase muscular development. However, there is an increased risk of developing hepatocellular carcinomas as supported by various case reports on such patients.[4,40-42]

Synthetic estrogens, specifically trans-diethylstilbestrol (DES), were used to prevent spontaneous abortion. It now appears that daughters born to the women who received DES have a 0.4% chance of developing vaginal carcinoma at the age of 14–22.[43]

There have been studies suggesting that endometrial cancers were increased in postmenopausal women taking estrogen, but other studies failed to show such an effect.[44,45] Nevertheless, several hundred well-documented cases of hepatic adenoma in women taking oral contraceptives have been reported. In most cases the tumors were benign or could be resected, but in some cases the tumors appeared more malignant.[46-48]

Other Drugs

For the past 5 years a combination of oral methoxypsoralen and exposure to ultraviolet light has been used to treat patients with psoriasis. It now appears that the relative risk of developing skin cancer in such patients is 2.6 times that of the usual population.[49,50]

Phenacetin, a component of analgesic mixtures, has been linked with tumors of the renal pelvis in patients who used these mixtures to excess.[51] However, one test of an aspirin-phenacetin-caffeine mixture in animals showed no neoplastic effect.[52] Other animal tests of phenacetin have been both negative and positive for carcinogenicity, and the matter is therefore open to discussion. Nevertheless, the IARC has placed *phenacetin* on the list of probable human carcinogens (see Table 1.1).[4]

Anticonvulsant drugs, including diphenylhydantoin and phenobarbital, have been implicated as the cause of excess lymphomas in patients treated with these compounds for epilepsy or related convulsive conditions. Since the risk is small, the balance may be tipped in favor of continuing to use these compounds in view of the beneficial effects. In animal studies diphenylhydantoin increased the lymphoma incidence in mice.[53]

Furthermore, phenobarbital has had a promoting action on the effect of other carcinogens in rats, depending on the dosage schedule. If given simultaneously with such carcinogens as nitrosodiethylamine or N-2-fluorenylacetamide, it inhibited their carcinogenic action. Given after the treatment with carcinogen, phenobarbital heightened any carcinogenic action.[54] In mice phenobarbital either reinforced the appearance of spontaneous tumors or evoked liver tumors.[4] However, the IARC concluded that diphenylhydantoin and phenobarbital could not be classified for their carcinogenicity in humans.

Reserpine has been implicated as a cause of breast cancer or perhaps other tumors in persons treated for hypertension. The picture is complicated because other factors—social class, obesity, type of diet, body build, etc.,—also play a role in breast cancer. However, the risk-benefit ratio in use of reserpine should be evaluated carefully.[4] To complicate the problem even more, studies of animals which were given much higher relative doses than patients receive showed that reserpine caused tumors in the test animals.[55]

Table 1.1. Chemicals Associated with Cancer in Humans.[a]

A. *Chemicals and Industrial Processes which are Carcinogenic for Humans*

Substance or Process	Site Affected and Type of Neoplasm	Confirming Animal Tests
4-Aminobiphenyl	Bladder — carcinoma	+
Arsenic and certain compounds	Skin, lung, liver — carcinoma	–
Asbestos	Respiratory tract — carcinoma Pleura & peritoneum — mesothelioma Gastrointestinal tract — carcinoma	+
Auramine manufacture	Bladder — carcinoma	Not applicable
Benzene	Blood — leukemia	–
Benzidine	Bladder — carcinoma	+
Bis (chloromethyl) ether and technical grade chloromethyl ether	Lung — carcinoma	+
Chlornaphazine	Bladder — carcinoma	±
Chromium and certain compounds	Lung — carcinoma	+
Diethylstilbestrol	Female genital tract — carcinoma (Transplacental)	+
Hematite mining (underground)	Lung — carcinoma	Not applicable
Isopropanol manufacture (strong acid process)	Respiratory tract — carcinoma	Not applicable
Melphalan	Blood — leukemia	+
Mustard gas	Respiratory tract — carcinoma	+
2-Naphthylamine	Bladder — carcinoma	+
Nickel refining	Respiratory tract — carcinoma	Not applicable
Soots, tars, and mineral oils	Skin, lung, bladder — carcinoma	+
Vinyl chloride	Liver — angiosarcoma Brain Lung — carcinoma Lymphatic system — lymphoma	+

B. *Chemicals which probably are Carcinogenic in Humans*

Substance	Site Affected (Human)	Confirming Animal Tests
Acrylonitrile	Colon, lung	+
Aflatoxins	Liver	+
Amitrole	Various sites	+
Auramine	Bladder	+

Table 1.1. Chemicals Associated with Cancer in Humans.[a] (continued)

B. *Chemicals which probably are Carcinogenic in Humans* (continued)

Substance	Site Affected (Human)	Confirming Animal Tests
Beryllium and certain compounds	Bone, lung	+
Cadmium and certain compounds	Kidney, prostate, lung	+
Carbon tetrachloride	Liver	+
Chlorambucil	Blood	+
Cyclophosphamide	Bladder, blood	+
Dimethylcarbamoyl chloride	?	–
Dimethyl sulfate	Lung	+
Ethylene oxide	Gastrointestinal tract, blood	±
Iron dextran	Connective tissue	+
Nickel and certain compounds	Respiratory tract	+
Oxymetholone	Liver	–
Phenacetin	Kidney, bladder	±
Polychlorinated biphenyls	Skin, various sites	+
Thiotepa	Blood	+

C. *Substances which may be linked to Cancer in Humans*

	Animal Tests
Chloramphenicol	No data
Chlordane/heptachlor	Limited
Chloroprene	Inadequate
Dichlorodiphenyltrichloroethane	Limited
Dieldrin	Limited
Epichlorohydrin	Limited
Hematite	Negative
Hexachlorocyclohexane (lindane)	Limited
Isoniazid	Limited
Isopropyl oils	Inadequate
Lead and lead compounds	Adequate
Phenobarbital	Limited
N-Phenyl-2-naphthylamine	Inadequate

Table 1.1. Chemicals Associated with Cancer in Humans.[a] (continued)

C. *Substances which may be linked to Cancer in Humans* (continued)	Animal Tests
Phenytoin (diphenylhydantoin)	Limited
Reserpine	Inadequate
Styrene	Limited
Trichloroethylene	Limited
Tris(aziridinyl)-p-benzoquinone	Limited

[a]Data from IARC.[4]

Chloramphenicol and phenylbutazone have been mentioned as possible causes of leukemia in patients treated with either of these drugs. However, confirmatory animal studies are not available.[4]

Congenital and Genetic Diseases

Abnormal chromosomes in humans are often associated with the development of neoplastic disease. Both the acute and chronic forms of myelocytic leukemia occur more frequently in persons with breaks or translocations in their chromosomes.[56]

Certain diseases, including ataxia telangiectasia, Fanconi's anemia, Bloom's syndrome, Kostmann's infantile genetic agranulocytosis, and glutathione reductase deficiency, all lead to an unusually high fragility of the chromosomes with a consequent excess of chromosome breaks. Individuals afflicted with any of these conditions are also more prone to develop cancer, especially leukemia. More than 80 Mendelian disorders which are complicated by a high probability of subseqeunt development of neoplasms have been tabulated.[56] The more well-known of these disorders include neurofibromatosis, retinoblastoma, neuroblastoma, pheochromocytoma, familial polyposis of the colon, Wilm's tumor, Paget's disease of the bone, malignant melanoma, xeroderma pigmentosum, and polycythemia vera.

A somewhat contrary situation—an excess of genetic material or chromosomes—is also deleterious. Several syndromes associated with extra chromosomes increase the risk of developing neoplastic disease. In Down's syndrome the leukemia rate is at least 11-fold higher than normal; in men with Klinefelter's syndrome the risk of developing breast cancer is 66 times that in normal men. Cryptorchidism increases the normal risk of developing a neoplastic disease by 30-fold.[56]

Congenital defects

The presence of Wilms' tumor, in childhood, is often associated with various defects including urogenital malformations, ear defects, eye defects, mental deficiency, and enlarged viscera. Retinoblastoma, especially bilateral, appears as a transmissible genetic disorder. This condition may lead to a high risk of bone tumors in survivors, an indication of an inherent susceptibility to certain types of cancers.[56,57]

Familial susceptibility

Aggregation or clustering of certain types of cancer in families has been well documented for several hundred years. A family history of a neoplasm may increase a person's risk for developing that neoplastic disease, depending on the neoplasm, 2 to many-fold. Increased susceptibility or common exposure to some known or unknown environmental carcinogen may occur. It now seems that a genetic component is involved in the origin of specific types of neoplasms. Different studies have indicated a 2 to 4-fold excess, compared with controls or the general population, of cancer of the stomach, uterus, lung, breast, and large intestine, childhood brain tumors, and sarcomas in relatives of cancer patients. Apparently, genetic component is also involved in the development of leukemia in siblings. Susceptible individuals in affected families tend to develop the same type of neoplasm in a single site or tissue system; different types of tumors may occur in other organs. The attributes of tumor specificity, early average age at onset, and a tendency for tumors to develop at multiple sites all point toward a genetic cause.[58,59]

Attempts have been made to link the enzyme aryl hydrocarbon hydroxylase with susceptibility to tumor development.[59] The variability in response between normal controls and patients precludes a definite correlation.