ANALYTICAL REVIEW

Recent Studies on the Etiology and Nature of Leukemia*

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So LIVELY is the race for a chemical that will cure leukemia that interest in research on the etiology and nature of this disease has waned. While it is true that control of a disease may be accomplished without knowing its cause, the control of leukemia is not yet in sight, and were its cause and nature known control measures might be found with greater ease.

Before the era of experimental leukemia several views had been advanced on its etiology and nature, based upon clinical and morphologic observations. The discovery of a filterable agent causing fowls leukemias (Ellerman, 1908) and tumors (Rous, 1911) led to the generalization that viruses are the immediate cause of perhaps all neoplasms. Subsequent investigations led to broadening of knowledge of both viruses and neoplasms, and although the virus theory soon became overshadowed by the highly productive research on carcinogenesis by chemicals, hormones and various types of radiation, the virus theory of leukemia and cancer remained among those firmly established. The view most widely held currently is that mammalian leukemias are neoplastic in nature and that, as other neoplasms, they may be caused by many agents, the action of which is modified by the genetic background and nutritional state of the host.1, 3

At variance with this concept several recent investigators have reopened the infectious theory of mammalian leukemia while others have proposed views reminiscent of “theories” abandoned long ago.

1. Causation of Mouse Leukemia by Virus

The discovery of the “milk” agent of breast carcinoma of mice (Bittner), now regarded to be a virus, led to search for a similar agent causing leukemia. The “milk” agent produces a true tumor without exhibiting features of an infectious disease. Although present in the blood and in many organs of apparently normal members of carrier strains, it is transmitted usually through the mother’s milk to her suckling offspring. Rarely, the father transmits the agent with his semen, “infecting” both the offspring and his mate.

Reciprocal crosses and foster nursing were employed in mice using high and low leukemia strains, and some maternal influence was evident (MacDowell et al. and others). In reciprocal crosses the male was found to transmit factors of susceptibility to leukemia, although not quite as well as the female (MacDowell et al. and Cole et al.). In foster nursing experiments the difference be-

* The term as used includes leukemia and all probably related diseases such as lymphoma and Hodgkin’s disease.

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tween the maternal influence in leukemia and in breast carcinoma was also marked. Mice of a low carcinoma strain when nursed by mothers of a high carcinoma strain acquired the agent of breast carcinoma, while the leukemia agent was not acquired under similar conditions. Unlike the Bitner agent for mammary cancer, which multiplies in the new host and once acquired is handed down to subsequent generations, the maternal influence of leukemia affects only the fostered generation.

While studying the nature of this resistance factor MacDowell and Taylor made the noteworthy discovery that this factor becomes intensified with aging of the mothers. They found that the resistance to leukemia conferred upon the offspring by low leukemia strain mothers, either before birth or through nursing, is not evident during their first pregnancies, when leukemia heredity shows full dominance, but is acquired by the mothers as their age increases. Accordingly, the percentage of leukemic offspring decreases as the parturition age of the mothers increases.

Gross inoculated mice of strain C3H (in which leukemia is rare) less than 10 hours old with extracts of leukemic cells and of normal embryos from mice of strain Ak (which has a high incidence of spontaneous leukemia) and found that several of the recipient mice developed leukemia. Similar inoculations were unsuccessful when the recipient mice were older than 12 hours. Gross concluded that the apparently spontaneous lymphoid leukemia of Ak mice is caused by a filterable agent similar to that of avian lymphomatosis. If correct, this would mark the most notable recent advance in leukemia research.

Whether or not these results are reproducible can be answered only by careful further work. At present this report is open to doubt. The experiments were done on a small scale and experimentation of this type is not without pitfalls. It is difficult to certify that a tissue extract is cell free. Very young C3H mice are highly susceptible to grafts of leukemic cells of Ak mice, and in experiments of others even young adult C3H mice were found to be susceptible to Ak leukemic cells. Furthermore, it is conceivable that C3H mice can accept grafts of primitive Ak cells with neoplastic potentialities. Success of grafts of leukemic cells depends on many factors, among which are the number of viable cells present in the inoculum, the route of entry and the inherited or acquired resistance of the host. When the number of cells in the inoculum is small the grafted cells appear to be dormant for many months and the latency period may approach that of spontaneous leukemia.

One of the arguments of Gross in favor of the viral induction of leukemia is the lack of tumor formation at the site of injection. Some types of leukemic cells may spread in the body and cause a systemic disease without forming a tumor at the portal of entry. This may be particularly true in the first few days of life. Such behavior does not indicate a basic difference between a common tumor cell and a leukemic cell, but is merely an expression of differences in the habitat and character of leukemic cells as compared with other neoplastic cells. Leukocytes are motile and their function calls for moving about in the body. Thus, it does not follow that leukemias are not neoplasms because they appear to start as a "systemic disease," simultaneously all over the body. A single or a few living leukemic cells introduced intravenously in susceptible hosts may
produce a systemic leukemia precisely of the type from which the injected cells were derived.

Natural transmission of the mammary tumor agent occurs through the mother's milk during the first few days after birth. The recent studies of Hummel and Little\(^8\) indicate that this agent disappears from the blood of C\(_3\)H\(^*\) females in late pregnancy and that the placenta is able to destroy or inhibit it. Once acquired the mammary tumor agent multiplies in and confers on the new host a high liability to develop mammary tumors, with relatively little respect to the genetic background of the agent's donor.

Heretofore, the results of genetic mating tests in mice were interpreted\(^1\) as indicating that the susceptibility to spontaneous leukemia is dependent on the percentage of leukemia heredity. There is no virus known with properties which can be reconciled with results of the genetic and nursing studies of leukemia. Should there be such a virus, the genetic studies might mean that: (a) the virus is transmitted by both parents (sperm and ovum) to all offspring, (b) the incidence of leukemia depends on genetic resistance factors acquired from the low leukemia strain and modified by nonhereditary factors.\(^1\) The first supposition is based on the existence of high leukemia strains, as that of MacDowell and Lynch line of the Ak strain, in which the incidence of leukemia exceeded 90 per cent, and on the observation that matings of Ak mice, which at time of death were free from leukemia, yielded offspring with about as high an incidence of leukemia as matings with Ak mice which died of leukemia. Support for the second supposition is lent by the observation that heredity from the low leukemia strain C\(_3\)H, used by Gross, inhibits much less the acquisition of leukemia potentialities inherited from the Ak strain than does that from the low leukemia strain RF.

In view of these considerations the work of Gross requires confirmation on a larger number of animals, the use of strains of mice as recipients which are resistant to grafts of the cells yielding the hypothetical virus, and proof that the inoculum is cell free.

Earlier (1938) experiments were described\(^1\), suggesting that mouse leukemia is transmitted by a filterable agent which is exceedingly sensitive to oxidation. The original publication was not confirmed by its authors or by others. The idea remains, but the facts are wanting.

None of the mammalian neoplasms transmissible by filterable agents have been found to be contagious. An exception is the papilloma of rabbits which appears to be infectious and, as Shope\(^9\) believes, is transmitted under natural conditions through the skin of the paw, perhaps by a vector.

2. Natural "Infection" by the Virus of Avian Lymphoma

The hypothetical virus of mouse leukemia is assumed to be similar to that of avian lymphoma.\(^7\) There is ample evidence that avian lymphoma and avian sarcoma are caused by viruses. Susceptibility of chickens to these viruses is not limited to the first few days of life, and adult birds readily develop a neoplasm upon injection with the specific virus.

\(^*\) The strain of mice in which this agent was discovered and which is most widely used in studying it.
Whether lymphomatoses (and avian neoplasms in general) are infectious and, if so, how birds acquire the virus have been the subject of much debate. 

Because of the practical importance of the “avian leukosis complex,” in 1938 a Regional Poultry Research Laboratory was established for its study in East Lansing, Mich. by the U. S. Department of Agriculture. Wisely, one of the major problems chosen for study was that of the natural spread of avian lymphomatosis. Earlier work had already established that all types of leukosis can be transmitted to adult chickens by filter-passing agents and that there are several different agents causing leukemia. Erythroleukosis and myeloleukosis proved most and lymphomatosis least readily transplantable and yielding the agent.

The extensive studies by Waters and Bywaters indicate that susceptibility to visceral lymphomatosis decreases gradually with age, but even chicks several weeks old are liable to acquire it through contact exposure to the specific virus. The incidence of lymphomatosis in experimental groups of chickens is dependent, among other factors, on the degree of exposure and the genetic resistance. The disease can also be transmitted from parent to offspring through the egg and presumably by indirect contact (Waters). The degree of lymphoid infiltration, increasing with age in the viscera of apparently normal birds, has been interpreted as possibly due to activity of latent viruses carried by the fowl (Lucas).

The technics used to purify, preserve and titrate other viruses have been improved and adapted to avian neoplasms (Claude, Kabat, Gottschalk, Bryan, Beard and their associates). By means of the electron microscope the erythroleukosis virus was visualized as a sperm shaped particle (Beard).

3. Cause of Hodgkin's Disease by Virus

Hodgkin's disease is notorious for the collection of varied infective agents which, from time to time, are described as its cause. So disappointing have been the new “discoveries” concerning Hodgkin's disease that some specialists came to view all new articles on its etiology with suspicious cynicism. Hodgkin's disease has anatomical and clinical features of both a neoplasm and an infectious disease, and it is natural that in this era of virus research investigators should utilize the subtle technics developed in the study of other viruses in attempts to find a virus that causes Hodgkin's disease.

One of the first noteworthy contributions in this field was that of Gordon who discovered in Hodgkin's tissue a filterable agent that caused in rabbits a nontransmissible encephalitis. Subsequent work has shown this not to be a virus but a substance present in the eosinophiles. The discovery of this toxic component adds still another factor to those complicating research on this disease. A toxic factor is also evident by causing generalized edema of the chick embryo when Hodgkin's tissue is injected into the chorio-allantois (Karnofsky et al.).

The alleged demonstration of viruses in mammalian tumors by growing them in the egg yolk (Taylor and Kynette) was the subject of a lively discussion at the AAA Research Conference on Cancer in 1943. These results were not readily reproducible by Taylor and associates, themselves, and could not be confirmed by Bryan and associates and Heilman. The possibility was considered that successful inoculations were due to the presence of living cells in the inoculum. Subsequently, the egg yolk technic has been used extensively by Taylor and
associates for the cultivation of neoplastic cells and for assay of potential chemotherapeutic agents, but not for the demonstration of viruses in mammalian neoplasms.

Recently, Lundback and Løfgren have obtained a filterable agent by successive passages of amniotic and chorionic tissue that had been inoculated with lymph nodes from Hodgkin's disease. An annotation in Lancet reviews this work, favoring the infectious view of Hodgkin's disease. Is this the long awaited agent of Hodgkin's disease and the technic to assay it? If not, where is the error in this experiment?

The control material which Lundback and Løfgren used for inoculation of chick embryos does not seem adequate. Past experience with this problem indicates the necessity of using varied control materials, both neoplastic and granulomatous, containing cells similar to those present in Hodgkin's tissues. Experience with the Gordon agent should be a reminder of the necessity of ample controls.

Grand described in cultures of tissues from Hodgkin's disease inclusion bodies, stainable with brilliant cresyl blue and with Seller's stain, and interpreted them as a manifestation of virus activity transferable to normal cells in tissue cultures. These findings still await confirmation.

Years ago viruses were defined as pathogens; now it is believed that viruses have a range of pathogenicity as wide as that of bacteria. Exclusion of carrier viruses poses a problem in several fields of research, e.g., tissue cultures may be contaminated by viruses in the plasma or organ extracts used as nutrients. In making "blind" animal or egg yolk passages for the purpose of enhancing the virulence of a hypothetical virus, carrier viruses can be easily picked up. Illustrative examples are the Nigg virus of mouse pneumonitis and the PVM virus of Horsfall. DeBruyn found a contaminating virus in the course of leukemia passages. The viruses of avian lymphoma are now believed to be common in apparently healthy birds. According to Blakemore, these viruses can produce simple inflammatory lesions in newborn chicks. This subject has been well analyzed by Duran-Reynals.

4. Disturbance of Balanced Production of Lymphoid and Myeloid Cells

The revival of Ziegler's idea of an "equilibrium disturbance" by Miller and Turner is based on the observations of Heinle and associates, who discovered (1942) that extracts and adsorbates of human urine produce myeloid hyperplasia and metaplasia in guinea pigs. Their most potent preparations were obtained from patients with chronic myeloid leukemia.

According to Foster and Miller there are two substances in the urine of patients with "leukemia and other lymphomatoid diseases," both considered to be "humoral hormones." A carbinol fraction of urine named lymphokentric acid causes lymphoid hyperplasia, while a noncarbinol fraction named myelokentric acid causes myeloid hyperplasia. They suppose that there is a reciprocal relationship between these substances; the excess of one causing lymphoid leukemia and

* The trend of considering myeloid and monocytic leukemias as "lymphomatoid diseases" is unfortunate, in my opinion. It introduces a bias, accepting as fact the monophyletic view that the lymphocyte is the mother cell of both granulocytes and monocytes.
that of the other myeloid leukemia. The lesions produced in guinea pigs by these substances are, however, not leukemic, and the specificity of their action requires further evidence.

Storer and Lushbaugh have produced lymphoid infiltration in guinea pigs with hepatic and splenic extracts from human lymphoma, but they found that mineral oil and other agents cause similar infiltrations. Hirschman, Heinle, and Wearn (1945) have purified this agent obtained from urine and determined some of its properties. The active principle found by them was protein or glycoprotein that differed in its chemical and physical properties from that of Turner and Miller. They believe that it is unlikely that the keto-acid of Turner and Miller exists in their preparation as a prosthetic group.

Recently, Foster and Miller assayed sera of leukemic patients by injecting it into the peritoneal cavity of guinea pigs in 5 cc. samples and studying the lymph nodes of the animals eight to forty-eight hours after injection. They found that serum from patients with chronic myeloid leukemia caused within twenty-four hours loss of lymphoid structure with fibrosis, by virtue of the contained myelokentric acid. These alterations are likened to those caused by cortisone or ACTH. Sera of patients with chronic lymphoid or monocytic leukemia and with Hodgkin's disease caused, on the contrary, lymphoid stimulation. These findings are interpreted as suggesting the presence in the blood of conjugates of both myelokentric and lymphokentric substances.

Miller and associates believe that the substances in question are present in normal hosts and that those with lymphomatoid have merely more of them. If the source of these substances is the respective blood cell, the greater number of blood cells in leukemias may explain the increased concentration of these substances and they need not be related to the genesis of the disease. Moreover, these substances have been found in normal beef liver (Turner and Miller). This organ may manufacture or yield such substances on cellular breakdown, or may store them as received from other organs or tissues.

The hypothesis of Miller and associates is incompatible with the experimental findings in several species of animals, indicating that the basic change in leukemia resides not in the host but in the leukemic cells which can be grafted on new hosts (if genetically compatible) in which they will proliferate without restraint. It is neither proven nor even likely that these substances are related to the etiology of the leukemias. Nevertheless, it is worthwhile to study substances stimulating or depressing hemopoiesis, as is now being done by Turner, to determine their source, chemical nature and biological significance.

5. Disturbance of Leukocytes Elimination

The idea that leukemia is due to a failure of normal elimination of leukocytes in the presence of their normal production was revived by Bierman and associates. Two types of experiments are described. In one the half life of leukocytes was estimated, on the basis of destruction rates by ultrasonic vibration, and it was found that the resistance of lymphocytes in lymphoid leukemia was markedly

* The reviewer would prefer to use the term "hemoblastosis" but hesitates to do so in this review since he desires not to introduce bias by stating categorically that all leukemias are neoplastic in nature.
increased as compared with that of normal lymphocytes. In the second type of experiment the ability of normal persons to destroy transfused leukemic leukocytes was studied, utilizing for sampling the venous catheterization technics. After cross transfusion of blood of leukemic and nonleukemic patients, they noted a decrease in leukocyte counts in the leukemic patients and absence of leukemia in the recipients. In their more recent studies the specific retention of cells by the lung of leukemic persons was reaffirmed. Accordingly, these workers concluded that the essential change in leukemia resides in the host and not in the leukemic cell.

Earlier Isaacs and Danielian postulated that elimination of lymphocytes occurs normally on mucosal surfaces of the oral cavity and intestinal tract and that alteration in leukocyte levels may result from a disturbance of this elimination mechanism.

The hypothesis of disturbed elimination or retention might well explain the leukocyte levels in leukemia, but the basic change in this disease is not that of blood invasion but of unrestrained proliferation coupled with retarded maturation.

Furthermore, this hypothesis ignores the following experimental findings:
(a) After massive perfusion into normal animals leukemic cells at first disappear from the blood and perfusion is followed by a period of latency. In susceptible animals the leukemic cells proliferate in tissues and ultimately reinvade the blood, while in resistant animals (after transient proliferation under favorable conditions) they are destroyed. These observations were made with myeloid leukemias of fowls in which the leukocyte counts frequently exceed one million, but leukemias of mammals may be expected to behave in a similar manner.
(b) Transmissibility of leukemia is successful only in genetically uniform and compatible animals. Is there any species more heterozygous than man? (c) Leukemia can be transmitted by a single cell or by a few cells in a genetically compatible strain of mice.

The Bierman theory implies the host's inability to destroy immature lymphoid cells. In the light of the above experiments, each leukemic cell would have to be assumed to carry with it a factor of resistance to the hypothetical removal mechanism and to hand it down to daughter cells indefinitely. If so, the leukemic cell may as well be called a neoplastic cell.

6. Transmission by Nucleoprotein or Chromatin Fractions of Leukemic Cells

The idea that leukemia and other neoplasms are caused by a change in the "chromatin" of the cell and can be induced in normal cells by the introduction of altered "chromatin" particles is supported by the recent experiments of Stasney, Cantarow and Paschkis. According to this idea, the "chromatin" particles of leukemic lymphocytes enter the nucleoprotein of the normal lymphocytes and induce a chromosomal change similar to that present in the leukemic cells from which they were derived. Similar ideas have fired the imagination of many brilliant investigators and met some support in recent experiments in both animal and plant kingdoms.

Stasney and associates fractionated cells from a transplantable lymphosarcoma of rat and from hepatomas, according to the technic of Claude and Potter,
and injected into the subcutaneous tissue the chromatin and mitochondria fractions. They noted the development of lymphosarcomas at the site of subcutaneous injection frequently followed by leukemia. As the authors state, proof of the absence of intact cells in these fractions is difficult, but they believe that such contamination is highly improbable and interpret their experiments as indicating transmission of lymphosarcoma by “chromatin” particles. Thus, while Gross conceives the agent transmitting leukemia akin to an infectious virus, Stasney and associates consider them to be self-reproducing particles of the cell.

The critical problem in the experiments of Stasney is how to prove the absence of living cells in the inoculum. When cell-free particles of lymphosarcoma of fowls are introduced in the subcutaneous tissue they must reach susceptible cells in order to render them neoplastic; the leukemias of fowls so induced start at common sites of lymphoid tissue and not in the subcutaneous tissue.\textsuperscript{11} The development of lymphosarcoma at the subcutaneous site of injected chromatin particles raises doubt that the inoculum in Stasney’s experiments was cell-free, although it does not exclude it, as lymphoid tissue can become established almost anywhere. Current work by these authors aims to clarify this problem.

7. The Induction of Leukemia by Ionizing Radiation

Leukemia can be readily induced in mice by common carcinogens. The report of Aubertin that leukemia is more common among radiologists than among physicians who are not radiologists provided the stimulus to attempt the induction of leukemia by x-rays. Although the data on the human are subject to criticism, the consensus is that exposure to x-rays does increase the incidence of leukemia in man.\textsuperscript{3} Preliminary indications reported from studies undertaken on the survivors of the atomic bombs at Hiroshima and Nagasaki in Japan, suggest that there is a substantial increase in the leukemia incidence rate in the exposed population over that found in a comparable control group.\textsuperscript{29}

Earlier studies carried out on thousands of mice have demonstrated that both lymphoid and myeloid leukemia can be readily induced by x-rays\textsuperscript{4} and more recently the leukemogenic power of different types of radiation and the factors and mechanism of leukemogenesis are subjects of precise and well-controlled experimentation.\textsuperscript{30-33}

In many strains of mice the most common type of lymphoma is that of the thymus; this occurs with or without associated involvement of the blood-forming and other organs. It was found that removal of the thymus before the onset of leukemia prevents the occurrence of thymic lymphoma and reduces the incidence of lymphoid leukemia.\textsuperscript{34}

Recent research conducted currently in several laboratories on the role of the thymus in the genesis of leukemia in mice seemed at first to be purely “academic” with no bearing on the genesis of human leukemia; it has, however, led to the discovery of a protective factor. Earlier experiments led to the conclusion that the effect of thymectomy was brought about by removal of the site of potentially malignant cells. Removal of the thymus will also prevent the induction of leukemia by x-rays (Kaplan\textsuperscript{27}) and by methylcholanthrene (Law and Miller\textsuperscript{35}). Hollcroft and associates found that irradiation of the whole body is
essential to bring about regression of lymphoma even when the tumor is irradiated with more than three times the whole body dose. Law and Miller observed that thymectomy reduces not only the incidence of thymic lymphoma but also that of leukemias other than those involving the thymus. These investigators concluded that the original explanation given for the mode of action of thymectomy, namely removal of the potentially malignant cells, may not be correct and that the thymus may be involved in leukemia induction through some indirect mechanism. The thymus is certainly under control of the adrenal cortex; administration of cortisone and testosterone inhibits induction of leukemia by x-rays. Both hormones cause involution of the thymus.

In following up the idea of the indirect role of the thymus Kaplan irradiated the upper and lower part of the body separately, compensating with increasing dosages for the reduction of the irradiated field. He found that the irradiation of either part of the body alone would not have the same leukemogenic effect as total body irradiation. He then exposed alternately the upper and lower part of the body and found that if this was done within one day the effect was nearly equal to that of total body exposure, but not if the alternation was done after three days.

The discovery of Jacobson that shielding the spleen or part of the intestine affords some protection to x-radiation is now common knowledge. He postulated that a humoral factor was responsible for this protection. Kaplan found that shielding one leg alone affords some protection. Simultaneously, Hilfinger and Ferguson noted that injection of bone marrow into irradiated rabbits likewise gives some protection. It is highly probable that the humoral factor of Jacobson is cellular in origin. Multiplication of the introduced primitive hemopoietic cells in irradiated hosts would assure a large supply of this protective substance. This supposition could readily be tested by measuring the degree of protection afforded by primitive marrow cells introduced into genetically compatible and incompatible hosts.

The protective effect was judged in Kaplan's experiments by the incidence of induced leukemia, in those of Jacobson by the increase of LD-50, and in those of Hilfinger and Ferguson by a more rapid recovery of the hemopoietic systems. Protection against radiation death is at present a highly productive field of research. Reduction of O2 tension is known to prevent acute lethality as are numerous substances (cysteine, BAL, glutathione, sodium cyanide, alcohols, etc.). It seems desirable to extend such experiments to studies of protection against induction of leukemia and other neoplasms.

8. Leukemia—a Deficiency Disease

Of all views that which assumes that leukemia is due to a maturation defect is the one most pleasing for its pursuance may at least contribute to knowledge of the physiology of hemopoiesis. The therapeutic agents thus far used (such as pterins and hormones) or the finding that leukemic cells are deficient in an organic or inorganic matter (as zinc) do not distinguish the leukemia from accepted neoplasms. Maturation of leukemic cells in vitro or in normal hosts would do so, but the best documented studies (such as those of M. R. Lewis, G. O. Gey, etc.)
and W. M. DeBruyn et al. have shown that leukemic cells multiply in vivo and retain their distinguishing individual features.

Transformation of leukemic myeloblasts into macrophages, as described recently from Sir Lionel Whitby's laboratory, contradicts observations of others with tissue cultures and, therefore, needs documentation (e.g., by motion pictures). Macrophages are present in practically all tissues, normal and malignant, and often survive in vitro when other cells die.

The spirited discussion by Sir Lionel Whitby is based on "clinical facts" and unfortunately ignores the vast amount of experimental data on leukemia of animals accumulated during the past two decades. It is beyond the scope of this review to engage in a verbal debate of interpretation of clinico-pathologic "facts" which are but mere appearances amenable to different explanations. Most of those who have had personal experience with experimental leukemia of animals and have attempted to bring experimental, clinical and anatomical "facts" into a perspective where the nature of the disease could be viewed have accepted the neoplastic theory.

9. The Reviewer's Understanding of the Etiology and Nature of Leukemia

The reviewer's resume of present knowledge of the nature of leukemia is as follows: the essential change in leukemia resides in the leukemic cell and consists of an acquired inability of immature leukocytes to respond to forces normally regulating their proliferation and maturation. This change is essentially that termed neoplastic; the end result is a new type of cell with a wide range of fixed abnormalities as concerns behavior and appearance.

The causes of this change are manifold. Widely different chemicals, including hormones, and physical agents, (x-rays, gamma rays, beta rays, slow or fast neutrons), can produce this change in lymphoid and probably also in other types of hemopoietic cells. Virus-like agents may cause some cancers in some mammals. They are the usual cause of leukemia in fowls, and there is no reason why similar agents might not cause leukemia in mammals, but the reports describing a leukemia virus in a mammal are not convincing. It is uncertain whether viruses that are the immediate cause of some malignant neoplasms are also their maintaining cause, but cells rendered neoplastic by viruses usually carry with them the causative virus. It is certain that viruses causing tumors can be acquired; it is uncertain whether they can arise de novo in avian or mammalian cells.

Many comments made in this review may be unjustly critical. Should further experimental or theoretical analysis of available data prove them to be wrong the questioned thesis will only gain in strength. However, should the comments prove to be meritorious they may serve as a brake to the hasty entry of newer "theories" into textbooks and into the daily press, and may help to channel research in sounder directions.

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