Recent Results in Cancer Research

STRATEGIES IN CLINICAL HEMATOLOGY

Edited by R. Gross & K.-P. Hellriegel

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Preface

Our present knowledge in the fields of both experimental and clinical hematology has rapidly progressed because of the complementary aspect one offers the other. In light of the above, basic research is a prerequisite for both diagnostic and therapeutic advances. Thus it would seem justified to review the pathogenesis of hemoblastoses and the experiences resulting from those animal experiments which are transferable to human conditions.

The association of Epstein-Barr virus infection with Burkitt's lymphoma appeared to be a model for the viral etiology of human neoplasias, the subject of many decades discussion. Although there is evidence for the correlation, the exact role of the virus in the etiology of the disease still remains to be clarified. In public, attention has been focused on the induction of neoplasia by environmental factors. For the hematologist the induction of hemoblastoses by immunosuppressive and cytostatic drugs gains increasing significance as a result of the wider use of these agents – not only cytotoxic cancer therapy, but also in treating autoimmune diseases and in managing transplantation problems. Physiology of the human stem cell has been intensively studied, and the presently available in vitro tests are of clinical use and enable greater understanding of pathophysiology, especially that of aplastic anemias and leukemias. Immunologic and biochemical markers have been of value in leukemias and malignant lymphomas, both as diagnostic tools and as prognostic parameters. Therapeutic effects may be expected from recent developments in stem cell physiology and the use of antisera against leukemic cells.

In acute lymphoblastic leukemia, the results achieved by pediatricians have been so encouraging that 5-year survival or even cure appear attainable in the near future in most children. Hematologic centers now procure complete remission in 50%–70% of adult patients with acute leukemia — figures that were unimaginable some years ago. At present, prolongation of the first remission appears to be of even

greater scientific relevancy than remission induction therapy itself. Improved classification, diagnosing, staging, treatment, and — above all — interdisciplinary cooperation have been extremely helpful in overcoming a certain stagnation in the management of malignant lymphomas.

Three topics related to erythropoiesis have been selected for inclusion in this volume: hereditary red cell enzyme abnormalities, iron overload, and porphyrin metabolism. Hereditary red cell enzyme abnormalities are interesting, not only because of recently discovered enzyme disorders but also because of the relationship between molecular abnormalities and red cell dysfunction. In iron metabolism the homeostatic mechanisms controlling iron absorption is one of the most fascinating aspects of research. Iron overload may be caused by increased absorption, either due to ingestion of large amounts under special conditions or to metabolic disorders, or by parenteral administration of iron, most frequently following multiple red blood cell transfusions. Investigation of the pathobiochemistry of porphyrins and porphyrias is a further excellent example of the stimulating interaction between basic research and clinical medicine.

In the pathogenesis of arterial thrombosis, interactions of blood components with the vessel wall are becoming more and more elucidated. From the studies of arterial thrombosis a new understanding of atherosclerosis seems to emerge. Hypercoagulability most probably contributes to an increased thrombotic tendency, but as yet a prethrombotic state cannot be recognized through the investigation of the platelets and the coagulation system. Von Willebrand's disease is more complex than the other inherited hemorrhagic diatheses. Besides autosomal recessive and autosomal dominant inherited forms, variant subtypes and an acquired von Willebrand's disease have been characterized. Studies on the factor VIII complex have contributed considerably to our understanding of this bleeding disorder.

These subjects were dealt with in the main lectures of the 5th Meeting of the European and African Division of the International Society of Haematology, held in Hamburg in August 1979, which brought together experimental and clinical investigators from all continents. The aims of the meeting were to establish new contacts, to deepen old friendships, and to contribute to better understanding and cooperation between individual scientists as well as between research groups.

June 1979

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Contents

Viral Etiology of Diseases of the Hematopoietic System

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In 1968 the Epstein-Barr virus (EBV) was identified as the causal agent of infectious mononucleosis [4]. Eleven years later a number of questions still remain unresolved:

1) In which *cells* does the virus replicate? There is little doubt that specific cells of the oropharyngeal region support EBV replication since transforming virus may be recovered from the saliva of infected patients and from healthy virus carriers. Nevertheless, the exact site of virus replication has not been identified. Suggestive evidence has been obtained that epithelial cells, possibly derived from the nasopharyngeal region, support EBV replication [8].
2) Which *host factors* determine the pathogenesis of EBV infection? A schematic outline of current concepts was presented earlier [13]. According to this model, after initial replication in nonlymphocytic cells the virus infects B-lymphocytes, which are transformed into lymphoblasts and express new surface properties. This in turn leads to a T-cell response directed against the transformed lymphocytes, which eventually should limit the course of the disease.
   Two lines of evidence supporting this view exist: EBV-transformed B-lymphoblasts are readily recovered from patients with infectious mononucleosis and grow indefinitely in tissue culture. Special chemical inductors permit the recovery of infectious EBV from such cultures [15]. Secondly, connatal or acquired T-cell deficiencies lead, upon EBV infection, to massive proliferation of transformed B-lymphoblasts resulting in a chronic and sometimes fatal infectious mononucleosis. An X-linked inherited immune defect described recently by PURTILO and co-workers [9], the X-linked lymphoproliferative syndrome, reveals this typical symptomatology upon EBV infection of patients. Other factors that may determine the course of the disease are presently unknown.
3) Considerable controversy exists on the mode of *viral genome persistence* in asymptomatic carriers. It is well-established that virtually every EBV infection leads to lifelong persistence of some viral genomes in some B-lymphocytes of the individuum. It is by no means clear, however, whether EB viral DNA persists in a genetically silent form without expression of any virus-specified antigens or whether, for example, the nuclear antigen EBNA is expressed in such cells and whether they reveal a transformed phenotype. The regulation of viral genome persistence is another phenomenon that is largely not understood.

The interest in EBV infections mainly originates from its involvement in two human malignant tumors: Burkitt's lymphoma and nasopharyngeal carcinoma (NPC). In Burkitt's lymphoma there is indeed evidence for a role of this virus in the etiology of the tumor:

1) The African tumor patients reveal approximately ten fold higher titers against EBV-related antigens than age-matched controls.
2) Viral DNA is demonstrable in the majority of such tumors, persisting without virus particle production.
3) The tumor cells contain the virus-specified nuclear antigen EBNA.
4) Early infections by EBV resulting in high anti-EBV titers have been shown to represent a significant risk factor in the development of Burkitt's lymphoma.
5) The virus induces malignant lymphoma and/or lymphoproliferative disease upon inoculation into Cottontop marmosets and owl monkeys. From such tumors EBV can be reisolated and shares its biologic properties with the original input virus.

Considering these data in the light of Koch's postulates, they largely fulfil the requirements for establishing the causal role of an agent in a specific disease. Nevertheless, some disturbing aspects which do not seem to support a straightforward role of EBV in Burkitt's lymphoma should not be ignored:

1) A number of Burkitt's lymphomas diagnosed outside of Africa reveal the same histologic features, yet they lack demonstrable EBV DNA and do not reveal the nuclear antigen EBNA. The percentage of such lymphomas amounts to about 75% of all Burkitt's lymphomas diagnosed outside the African tumor belt. Only 25% contain EBV DNA and EBNA antigen.
2) Even in endemic regions of Africa approximately 5% of the tumors seem to lack EBV DNA and EBNA.
3) Both EBV genome-containing and EBV-negative tumors show the same chromosomal aberration, a reciprocal translocation involving the terminal segments of chromosomes 8 and 14.

In view of these data it is difficult to maintain an unifying concept for an EBV-induced etiology of Burkitt's lymphoma. There can be little doubt that the virus plays some role in Burkitt's lymphoma induction, but it becomes increasingly difficult to decide which.
One way out of this dilemma could be the postulation of two different etiologies, one by EBV, the other by a different factor, emerging eventually in an histologically identical picture. Although I favored this view for a number of years [12], it is barely possible to reconcile it with the recent demonstration of the same specific chromosomal aberrations in EBV-positive and negative tumors. In addition, a plausible explanation for the geographic clusters would be difficult to derive from such speculations since EBV infections (and even infections early in life) are common all over the world, although in part dependent on living conditions. Even holoendemic malaria infection in the African endemic regions, as observed by BURKITT [1], does not provide a satisfactory answer, since other regions exist with similar epidemiologic situations as far as malaria and EBV infections are concerned (e.g., the Amazonian region), but apparently without a comparable incidence of Burkitt's lymphomas.
In order to circumvent these problems we recently proposed a different role of EBV in the induction of such tumors, designating this the "target cell conditioning model". According to this model EBV infection, particularly if occurring at a very young age leads to an enhanced proliferation of B-lymphoblasts. This should be even more pronounced if malaria infections take place concomitantly. The intensive temporary proliferation of lymphoblasts should provide the target cell pool for a subsequent event, visualized as a different tumor virus infection, which "supertransforms" at least some of the proliferating lymphoblasts and would provide the cells for later lymphoma development. This secondary infection would be

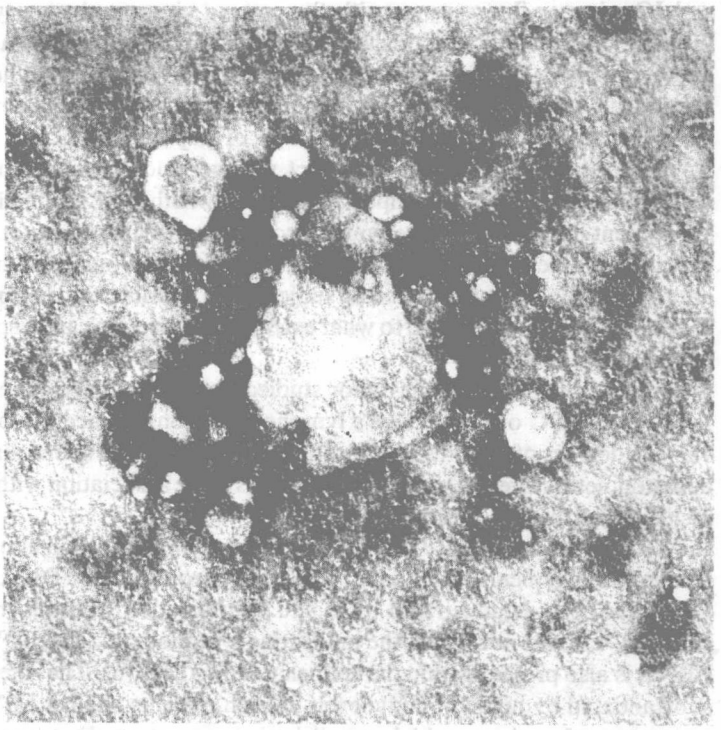

Fig. 1. Papovavirus particles from African green monkey lymphoblasts

mediated by a hypothetical lymphotropic agent that would depend on proliferating lymphoblasts for its infection.

We are greatly encouraged by the isolation of a papovavirus (Fig. 1) from African green monkeys that seems to require the postulated host range [13]. This virus was isolated from a lymphoblastoid line derived from a lymph node of an apparently healthy animal. It grows exclusively in B-lymphoblasts of such animals, but also in an EBV-free line of human B-lymphoma cells derived from an African EBV-negative Burkitt's lymphoma. Serologic and biochemical characterization of this virus proved that it represents a hitherto unknown papovavirus belonging to a group of DNA viruses which seems to contain exclusively oncogenic agents. Although the biologic role of such papovavirus infections has not yet been clarified, it appears to be of considerable interest that agents exist which depend for their replication on stimulated and proliferating lymphoblasts. Moreover, seroepidemiologic studies revealed that the majority of African green monkeys tested possess antibodies against this virus.

An intensive search for similar agents in human cells has recently been successful [13]. Typical papovavirus particles were detected in a human lymphoblastoid line derived from an 11-year-old boy with acute lymphatic leukemia. This agent appears to differ from the monkey virus serologically: sera from African green monkeys reacting with the African green monkey virus fail to react with these human cells. In addition, a number of human sera stain some nuclei of cells of this human line without reacting with the African green monkey virus. SV40 T antisera, which cross-reacts with T antigens of the two known human papovaviruses, BK

and JC, give no fluorescence with the papova virus-producing lymphoblasts. Although a further characterization of this agent is still not available, the data suggest that it represents another member of the papovavirus group with a lymphotropic host range. Probably these agents (the African green monkey papovavirus and the isolate from human cells) will have to be classified as a new distinct subgroup of papovaviruses.

At present it is not possible to predict whether such isolates could play a role in human malignant disease. It is also impossible to state whether EBV infections are a precondition for subsequent infection by these lymphotropic papovaviruses or not. It should be emphasized that the cell line in which the virus has been detected has been grown in tissue culture for approximately 11 years, thus being subject to all possible kinds of exogenous contaminations. Future studies have to reveal to what extent such infections are responsible for diseases of the hematopoietic system.

One other human malignant tumor studied extensively in relation to a possible etiology by EBV is the NPC or Schmincke's lymphoepithelioma. Since it represents a carcinoma with varying degrees of lymphatic infiltrations it may not belong in a discussion of diseases of the hematopoietic system. On the other hand, its close association with EBV infections justify its inclusion in this discussion.

In NPC the presence of EBV genomes can be demonstrated in almost 100% of the cases. All histologically typical tumors have been found to contain EBV DNA (see reviews [12, 15]). The DNA has been demonstrated by in situ hybridization methods in the epithelial carcinoma cells [10, 11] and not within the infiltrating lymphocytes. The EBV-specific nuclear antigen EBNA is also present within the epithelial tumor cells [6]. The role of EBV in NPC is further substantiated by high antibody levels in such patients against EBV-specified structural and nonstructural antigens which parallel to some extent the tumor burden [5].

Although there is good reason to ascribe specificity to the association of EBV infections with NPC, its exact role in the etiology of this disease is difficult to determine. This is mainly due to the lack of an animal system for the induction of similar tumors and the non availability of tissue culture cell lines derived from this tumor. It became possible in recent years to heterotransplant NPC cells into nude mice and to serially passage such tumors under these conditions [7]. Although such tumors are valuable tools for virologic studies, they pose some problems in view of their contamination with murine xenotropic oncornaviruses [3].

No other viruses revealing a pronounced tropism to cells of the hematopoietic system have yet been identified. Although many viruses can infect lymphoblasts, and human cytomegalovirus may even persist in a specific fraction of hematopoietic cells, all these agents commonly infect different types of tissue and will not be included in this discussion.

To summarize the role of viruses in diseases of the hematopoietic system: EBV infections are commonly associated with Burkitt's lymphoma and NPC. It is obvious that EBV takes part in the etiology of Burkitt's lymphoma, although it cannot be the sole or even an essential factor. A hypothesis has been advanced that visualizes the lymphoproliferative response induced by EBV as a "target cell conditioning" for subsequent infections by other hitherto unknown lymphotropic viruses with transforming properties. Papovaviruses depending for their replication on stimulated, proliferating lymphoblasts have been discovered recently in lymphoblastoid cells derived from African green monkeys and from man. Their role in the pathogenesis of diseases of the hematopoietic system remains to be established.

References

1. Burkitt, D.: Etiology of Burkitt's lymphoma – an alternative hypothesis to a vectored virus. J. Natl. Cancer Inst. *42*, 19–28 (1969)
2. Clifford, P., de Schryver, A., de-Thé, G., Diehl, V., Klein, G.: Antibodies to Epstein-Barr virus in nasopharyngeal carcinoma, other head and neck neoplasms, and control groups. J. Natl. Cancer Inst. *44*, 225–231 (1970)
3. Crawford, D. W., Achong, B. G., Teich, N. M., Finerty, S., Thompson, J. L., Epstein, M. A., Giovanella, B. C.: Identification of murine endogenous xenotropic retrovirus in cultured multicellular tumour spheroids from nude-mouse passaged nasopharyngeal carcinoma. Int. J. Cancer *23*, 1–7 (1979)
4. Henle, G., Henle, W., Diehl, V.: Relation of Burkitt's tumor associated herpes-type virus to infectious mononucleosis. Proc. Natl. Acad. Sci. USA *59*, 94–101 (1968)
5. Henle, W., Henle, G., Ho, H. C., Burtin, P., Chachin, Y., Clifford, P., de Schryver, A., de-Thé, G., Diehl, V., Klein, G.: Antibodies to Epstein-Barr virus in nasopharyngeal carcinoma, other head and neck neoplasms, and control groups. J. Natl. Cancer Inst. *44*, 225–231 (1970)
6. Huang, D. P., Ho, J. C., Henle, W., Henle, G.: Demonstration of Epstein-Barr virus-associated nuclear antigen in nasopharyngeal carcinoma cells from fresh biopsies. Int. J. Cancer *14*, 580–588 (1974)
7. Klein, G., Giovanella, B. C., Lindahl, T., Fialkow, P. J., Singh, S., Stehlin, J.: Direct evidence for the presence of Epstein-Barr virus DNA and nuclear antigen in malignant epithelial cells from patients with anaplastic carcinoma of the nasopharynx. Proc. Natl. Acad. Sci. USA *71*, 4737–4741 (1974)
8. Lemon, S. M., Hutt, L. M., Shaw, J. E., Li, J. L. H., Pagano, S.: Replication of EBV in epithelial cells during infectious mononucleosis. Nature *268*, 271 (1977)
9. Purtilo, D. T., De Florio, D., Hutt, L. M., Bhawan, J., Yuang, J. P. S., Otto, R., Edwards, W.: Variable phenotypic expression of an X-linked recessive lymphoproliferative syndrome. N. Engl. J. Med. *297*, 1077–1081 (1978)
10. Wolf, H., zur Hausen, H., Becker, V.: EB viral genomes in epithelial nasopharyngeal carcinoma cells. Nature (New Biol.) *244*, 245–247 (1973)
11. Wolf, H., zur Hausen, H., Klein, G., Becker, V., Henle, G., Henle, W.: Attempts to detect virus-specific DNA sequences in human tumors: III. Epstein-Barr viral DNA in nonlymphoid nasopharyngeal carcinoma cells. Med. Microbiol. Immunol. *161*, 15–21 (1975)
12. zur Hausen, H.: Oncogenic herpes viruses. Biochim. Biophys. Acta *417*, 25–53 (1975)
13. zur Hausen, H.: DNA viruses in human cancer, biochemical approaches. Cancer Res. *36*, 414–416 (1976)
14. zur Hausen, H., Gissmann, L.: Lymphotropic papovaviruses isolated from African green monkey and human cells. Med. Microbiol. Immunol. (in press)
15. zur Hausen, H., Bornkamm, G. W., Schmidt, R., Hecker, E.: Tumor initiators and promoters in the induction of Epstein-Barr virus. Proc. Natl. Acad. Sci. USA *76*, 782–785 (1979)

Leukemias and Lymphomas Associated with the Use of Cytotoxic and Immunosuppressive Drugs

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The hematologist is intimately connected with the care of patients undergoing treatment with immunosuppressive or cancer chemotherapeutic agents, many of which have profound effects upon the bone marrow, lymphoid tissues, and the circulating blood. Most changes, such as leukopenia, thrombocytopenia, or anemia are usually reversible when treatment is stopped. However, sometimes progressive myeloproliferative or lymphoproliferative disorders may occur. In this report we shall be concerned mainly with the development of lymphomas in organ transplant recipients and leukemias in patients treated with cancer chemotherapy.

Lymphomas and Leukemias in Organ Transplant Recipients

Almost all organ transplant recipients are treated on a daily basis with azathioprine and adrenal corticosteroids, usually prednisone or methyl prednisone. Other agents which are sometimes used are cyclophosphamide and antilymphocyte globulin. Lymphocyte-depleting procedures which are used in some centers include splenectomy and thoracic duct drainage.

Lymphomas

An increased incidence of malignancy is observed in these patients [5–10]. Neoplasms occur 100 times more frequently than they do in persons of the same age range in the general population [5, 7–9]. There is a disproportionately high incidence of solid lymphomas. Up till February 1979 the Denver Transplant Tumor Registry had received data on 800 recipients of kidney, heart, or liver homografts who had developed 845 de novo types of cancer after transplantation. If we exclude patients with nonmelanoma skin cancers and carcinoma in situ of the uterine cervix, which are omitted from most surveys of cancer statistics, we are left with 526 patients of whom 170 (32%) had lymphomas. This contrasts with an incidence of 3%–4% in the general population [5, 7–9].

The lymphomas for the most part occurred in young patients, whose average age at the time of transplantation was 38 (range 5–70) years. The neoplasms appeared at a surprisingly short time after transplantation, ranging from 2 to 146 (average 27) months.

The types of lymphoma are shown in Table 1. There are considerable differences from those observed in the general population. Whereas Hodgkin's disease is the most common lymphoma in any age group in the general population, in whom it makes up 34% of all lymphomas

Table 1. Lymphomas in organ transplant recipients

Type of lymphoma	No. of recipients
Reticulum cell sarcomas	105[a]
Kaposi's sarcomas	27[a]
Unclassified lymphomas	20
Lymphosarcomas	10
Plasma cell lymphomas	4
Hodgkin's disease	3
Lymphoreticular tumors	2
Total	171

[a] One patient had a reticulum cell sarcoma and Kaposi's sarcoma.

[7–9], it constituted only 3 of the 171 lymphomas (1.8%) in the transplant patients. The predominant type was the reticulum cell sarcoma, which is 350 times more common in renal transplant recipients than in the public at large [2]. These tumors may represent an abnormal immune response to the foreign histocompatibility antigens of the homograft, as most tumors have morphological characteristics of antigen-activated lymphocytes and may be classified as "immunoblastic sarcomas".

In the general population the central nervous system is involved by lymphomas in less than 2% of patients. In contrast, lymphomas in transplant patients have a strong predilection for this area [5, 7–9] which was involved in 61 of 144 patients (42%) with non-Kaposi's lymphomas. Even more striking is the fact that the tumors were confined to the central nervous system in 52 of the 61 patients (85%). An important lesson can be gained from this experience. If a transplant recipient develops neurological symptoms, we usually consider causes such as hypertensive encephalopathy, meningitis, brain abscess, or intracranial bleeding, but we also should bear in mind the possibility of a cerebral lymphoma. A thorough diagnostic approach is indicated, which may include examination of the cerebrospinal fluid, electroencephalography, brain scan, cerebral angiography, and computerized cerebral tomography.

The histogenesis of Kaposi's sarcoma is controversial. As some investigators consider it to be a lymphoma we have included it in this category [8]. It is a rare tumor in the general population, in whom it makes up 0.6% of neoplasms [10]; in contrast it made up 27 of 845 tumors in transplant patients (3.2%). The incidence becomes 4.7% if we exclude from our calculations 274 nonmelanoma skin cancers and carcinomas in situ of the uterine cervix. Seventeen of the patients had lesions of the skin and/or the mucosa of oropharynx and nose, while ten (37%) had visceral lesions most frequently involving the alimentary tract and lungs.

Leukemias

In contrast with the high incidence of lymphomas in organ transplant recipients, the incidence of leukemias is only slightly increased (Table 2). These occurred in 21 of the 526 patients