A rapidly expanding lesion which produces a striking distortion and destruction of the mandible and facial bones in children has been recognized for at least half a century in East Africa (Fig. 1). An excellent clinical description of a typical case was found in the records of a mission hospital in Uganda for the year 1907, and most physicians who have seen service in East Africa readily recall the entity. However, the neoplastic nature of the disease process and its tendency to metastasize widely was not fully appreciated, at least in the published literature, until 1958 (1). In 1959, O’Conor and Davies recognized and identified the lesion in the jaws as but one manifestation of malignant lymphoma, which we reported to be the most common neoplastic disease in children in Uganda (11). Subsequently, the clinical and pathological features of 106 cases, chiefly from Uganda, were reviewed and described in more detail (3, 10). As a result of an unusual attention given to this subject by the lay press, certain aspects of the disease in Africa have been, perhaps, overemphasized and dramatized. With a great deal of speculation about viruses and insect vectors, based on preliminary and inconclusive epidemiological data, several less spectacular facts have been overlooked, facts which I believe are of significance, particularly to those who are interested in designing and initiating studies to define the environmental factors which may play a more indirect and probably complex role in the pathogenesis of lymphosarcoma in this and in other human populations.

**CLINICAL ASPECTS**

A brief review of the outstanding clinical features and the histopathological characteristics of malignant lymphoma in children in Africa is pertinent to the ensuing discussion. These clinical features are summarized in Table 1. From birth to age 15, the distribution curve is bell-shaped with a peak between 6 and 7 years. This characteristic age distribution has been noted in the published series from Uganda (3, 10) and in the 190 cases reported by Dalldorf from Kenya (4). Lymphoma after the age of 14 is rarely seen in Africa until the mid-twenties, where there is a slow rise to a maximum in the 4th or 5th decade, which is similar to the age distribution in other countries.

In somewhat less than half of the recorded cases the patient presents with one or more large swellings in the mandible, the maxilla, or the orbit. At the time of initial examination tumor deposits can
usually be found at other sites in these children. An almost equal number of cases seek medical treatment because of an abdominal mass and symptoms which vary depending on the size and visceral location of lymphomatous tumors. These are frequently retroperitoneal but may be renal, ovarian, or in various parts of the gastrointestinal tract. Large tumor formations at other sites, such as the salivary glands, subcutaneous tissues, long bones, thyroid, testicle, and spinal cord, provide the initial presentation in 10–20 per cent of the cases. In only the rare case is peripheral lymphadenopathy due to the neoplasia an important feature. A small percentage of the cases with a presenting complaint not related to tumors of the facial bones or the orbit may show some clinical evidence of tumor at these sites, or they may subsequently develop such lesions, but as a rule those with large presenting tumors elsewhere will not have detectable concomitant tumors in the jaw.

Although tumor deposits may sometimes be found in the bone marrow, and occasionally the spread of neoplastic cells is diffuse, a peripheral blood manifestation of leukemia was not seen in our series or in any other cases reported to date.

Finally, the disease takes a rapidly fatal course. In the typical case, the parents of the affected child will state they have noticed the swelling in the face or that the child has complained of abdominal pain for only a few weeks. Unless treated, the children are usually dead within 12 months.

Pathological Aspects

I will not dwell on the descriptive morbid anatomy of this tumor, but certain points related to the gross and histologic appearance should be emphasized. At autopsy the tumor has been found in virtually every organ and tissue in the body. The predilection for the bones of the jaws and face has been noted. Although peripheral lymph node enlargement is not marked, large retroperitoneal, celiac, and periaortic masses probably have their origin in lymph nodes. The kidneys, the gonads, the liver, the thyroid, and salivary glands are common sites for tumor, whereas involvement of the lungs, mediastinum, and spleen is relatively infrequent. In the only autopsy series reported to date (10) every case with involvement of the jaws also had tumor at distant sites, and the distribution in other organs was similar whether or not the jaws were involved. The histologic appearance of these lymphosarcomas, illustrated in Figure 2, is relatively uniform in all cases, with only minor variations in cell size, degree of differentiation, amount of stroma, and number of histiocytes. Furthermore, it should be stressed that the microscopic sections of tumor from jaw and nonjaw cases are histologically indistinguishable.

Role of Geographical Pathology

Geographical pathology is the comparative study of disease patterns or of a specific disease in different geographic areas with an aim to search out environmental factors that may be related to demonstrated variations in these patterns. In cancer research the ultimate purpose is to better understand the mechanism whereby given environmental factors affect the process of oncogenesis. In reference to the disease under discussion, one must face the immediate question: How does lymphosarcoma in children in Africa differ from lymphosarcoma in children in Europe and America? First, it is important to keep in mind that the African disease is in fact a lymphosarcoma and that it is essentially the same disease called by that name elsewhere. Next, one must define as precisely as possible those features which make malignant lymphoma in African children of particular interest—not to the reader of the Sunday supplement or the television audience, but to the geographical pathologist and cancer investigator.

Comparative Frequency

Incidence rates for cancer are not yet available in that portion of Africa where childhood lymphoma is commonly seen. This lack makes it impossible to compare accurately the figures in Africa with those in more developed areas. However, ratios of lymphoma to total cancer in children, and the absolute number of cases seen per year, indicate an unequivocal and striking frequency of this neoplasm. The 106 cases published from Uganda were seen over an 8-year period, and the series reported from Kenya are said to represent only a 5-year experience. Both groups were histologically proven cases and by no means represent a total registration of all instances of the disease in the two countries. In the United States, and in most other countries, lymphosarcoma in children is, by
contrast, quite a rare disease, and even in the large hospitals specializing in cancer or pediatrics no more than one or two cases will be seen in a year. At Memorial Hospital for Cancer in New York, where patients are drawn from all over the world, only 41 cases were recorded in thirty years (5). At the Clinical Center of the National Institutes of Health, where there is a preponderance of patients with leukemia and lymphoma, there are only seven cases of childhood lymphosarcoma in the autopsy files for the 10 years that the Center has been open. At Children’s Hospital in Washington, also with an active chemotherapy service and many cancer admissions, and where there is a very high post mortem follow-up, only three cases of nonleukemic lymphosarcoma in childhood were found in 10 years of autopsy records. A high incidence, therefore, is one of the most outstanding differences between lymphosarcoma in African children and the same disease elsewhere. It will perhaps be many years before adequate medical services and accurate census data are realized in the African countries, and until then significant and meaningful comparisons of incidence rates with highly developed countries cannot be made. I do not believe, however, that the utilization of information based on what appears to be valid clinical impressions need delay pertinent investigations until these impressions have statistical confirmation.

**Clinical Comparison**

In Table 1, I referred to four clinical features which are important in the characterization of malignant lymphoma in African children: age distribution, site of initial presentation, absence of leukemic manifestation in peripheral blood, and the course of the disease. Although the infrequency of childhood lymphoma outside of Africa, already emphasized, limits the experience of most physicians, the rapid growth and early fatal outcome of the tumor is accepted by all and needs no further comment. Similarly, the propensivity of this disease in children for visceral involvement and to present initially in primary sites other than the peripheral lymph nodes has been noted by others.

A palpable abdominal mass, with symptoms referable to the abdomen or pelvis, is probably the most frequent presentation of lymphosarcoma in children in the United States. What is not seen, except with extreme rarity, outside of Africa and parts of New Guinea, is the extensive involvement of the jaw and facial bones by tumor and its frequent extension into the orbit. Although this manifestation of the disease has been reported in other parts of the world (5, 6, 8, 9, 12), and I have seen histologic material on several such cases in the United States in the last 2 years, there can be no question that in central Africa the disease has an overwhelming predilection for these unusual sites. This, then, is the second important difference between the manifestation of childhood lymphoma in Africa and elsewhere. Nevertheless, it must not be forgotten that although this curious predilection for the jaws in Africa is an important difference, more than half the cases in Africa do not have such involvement and are indistinguishable in every other way from lymphosarcoma in children anywhere else.

Arrival at a discussion of age distribution and the appearance of leukemic cells in the peripheral blood necessitates a consideration of the relationship of leukemia and lymphoma. In those parts of Africa where the typical lymphosarcoma cases are seen so frequently, leukemia is conversely rare. In most other areas of the world leukemia is the most common neoplasm of childhood, and many cases initially diagnosed as lymphosarcoma may develop a leukemic peripheral blood sometime during the course of the disease. A speculative digression into the possible significance of these observations, and the nature of the relationship of the two diseases, is well beyond the scope of this presentation. However, two facts which have a bearing on this question will be cited.

It has already been noted that the African lymphoma is a nonleukemic disease and has a peak in the age-distribution curve between 6 and 7 years. The age curve for leukemia in children in the United States, on the other hand, peaks at about 4 years and drops off very rapidly thereafter. The relative rarity of lymphosarcoma in children in the United States precludes collection of large numbers of cases, but if one selects only nonleukemic cases of lymphosarcoma, so as to eliminate those which might be, in fact, leukemia with extensive visceral infiltration, an unmistakable resemblance to the African disease can be seen. Fourteen autopsied cases of lymphosarcoma in children have been studied recently. These represent all the nonleukemic lymphosarcomas in children from three large hospitals which specialize in the care of malignant disease. The mean age of these fourteen children was 7.4 years. Eleven were brought to the physician with abdominal symptoms and signs of an abdominal mass; two had large tumors in the submandibular and postauricular area; and one had a massive tumor involving the anterior chest wall. All had a very short clinical

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*G. Guin, personal communication.

*R. E. J. Ten Seldam, personal communication.*
history and a rapidly fatal course. At autopsy, widespread retroperitoneal and visceral involvement similar to that in the African cases was found. This is admittedly a small number of cases, but they do serve at least to illustrate that the so-called African lymphoma is not a new disease or one peculiar to that continent.

**Histologic Comparison**

Nomenclature and classification of tumors are ultimately based on histologic interpretation. The African tumor is histologically a lymphosarcoma by all ordinary criteria, and any confusion regarding this terminology or objection to its use can be attributed to semantics. Although the uniformity in the microscopic appearance of the African cases, and the starry-sky effect produced by numerous phagocytic cells, have been considered distinctive (7), I should like to point out and particularly emphasize that these histologic features are not peculiar to the African cases but merely characterize lymphosarcoma in children generally and occasionally are seen in tumors of adults as well. I think this is an important point and one not fully appreciated because the disease is so infrequent outside of Africa. In all the cases from the autopsy service of the Clinical Center at the National Institutes of Health, the histologic pattern is similar, and the sections are indistinguishable from the African material. Figures 3–8 are a composite of microphotographs of six N.I.H. cases, and the histologic appearance at low power can be compared with the typical African case in Figure 2. Two African and two American cases are illustrated at higher magnification in Figures 9–12. It has previously been noted that in Africa the jaw and nonjew cases are histologically identical, and now it can be seen that they, in turn, are identical to cases of childhood lymphosarcoma outside of Africa.

**DISCUSSION**

Nonleukemic lymphosarcoma in children in Africa and elsewhere has thus been shown to be similar in age distribution, clinical symptomatology and manifestation, clinical course, and histologic appearance. The disease in Africa has likewise been shown to differ in only two important ways: an unusually high frequency and a striking predilection for the bones of the jaw and face. Unlike many of the previous publications on this subject, I have not in this instance characterized the African disease by its geographical distribution. Rather I should prefer to place the emphasis somewhat differently and state that the two single features wherein the African disease differs from lymphosarcoma elsewhere show a definite geographical pattern and that both these features, the high incidence and jaw predilection, apparently have the same geographical distribution.

Using clinical observations of “jaw tumor” as an indicator of the occurrence of the disease, Burkitt has defined a “lymphoma belt,” which extends across central Africa but fades off in a north and south direction (2). I do not wish to go into the details of his epidemiological studies except to state that he has related the occurrence of the disease to low altitude and high humidity. He has interpreted these observations as evidence for a mosquito vector and the possibility that a virus is the etiologic agent. This is an attractive theory, and there are certainly experimental models of virus-induced blood dyscrasias in rodents and fowl which can be used to support it. It is a difficult task, however, to prove that such an insect and virus relationship are involved in the human problem. Several teams of scientists from Europe and the United States have made virus-hunting safaris to Africa, but to my knowledge there has as yet been no major breakthrough. Work along these lines will undoubtedly continue.

If, however, as the evidence suggests, lymphosarcoma in Africa is essentially the same disease as elsewhere, it is more logical to assume that the role of any parasite or virus will not necessarily be that of a direct etiologic agent but, rather, one which enhances the susceptibility of the host for the ultimate development of lymphosarcoma. The striking frequency of the disease in Africa and its odd propensity for growth in the jaw, which are the principal if not the only differences from lymphoma in children elsewhere, furthermore suggest not only an altered host susceptibility in general but an increased susceptibility or response of a particular anatomic part of that host.

The fact that these differences in the African disease follow the same geographical pattern is a fortunate experiment of nature which provides a focal point for studying possible environmental factors, whether they be parasites, viruses, or whatever else, which might explain this altered host reaction.

Speculation and theory are only of value if they lead to productive thought and to confirmation or rejection of a hypothesis by experimentation. Little or nothing is known about the condition of the mouth in African children or the diseases which may particularly affect the oral cavity and the adjacent hard and soft tissues. No systematic pathological examination has been made of the jaws and facial bones of the children in the so-called “lymphoma belt” to see how much lymph-
oid tissue is present, whether it tends to be hyperplastic, and, if so, what stimuli are responsible. Although there is considerable information about disease patterns in various parts of Africa, these patterns have not been studied with any thought as to how they may affect the manifestation of a single malignant disease; nor has any particular attention been directed to the epidemiology of those non-neoplastic diseases which specifically affect the lymphoreticular tissues. Here, then, is a problem in the geographical pathology of cancer which probably cannot be solved by the virologist alone and which demands coordinated effort by scientists trained in many disciplines. Comparative epidemiological studies of the endemic diseases in high- and low-risk populations and concomitant pathological studies with particular attention to the jaw and lymphoreticular system are suggested as an alternative, or at least as an associated effort to be added to the direct virus approach. Geographical pathology, if it is to be a productive area in cancer research, must be experimental pathology in the broadest sense. Those interested must not confine themselves to cancer registration and calculation of rates. Positive experiments inside the laboratory and out, and experiments on human material as well as on animals, must be designed and pursued after the problem in question is well defined and properly understood.

REFERENCES

Figs. 3-8.—Six cases of nonleukemic lymphoma in children in the United States. The "water pot" effect is evident in all, ×150.

Fig. 3.—7-year-old-white female.
Fig. 4.—5-year-old Negro male.
Fig. 5.—11-year-old white male.
Fig. 6.—7-year-old white male.
Fig. 7.—7-year-old-white male.
Fig. 8.—8-year-old white female.
Figs. 9-12.—Comparative histopathology of lymphoma in African and United States cases at high power, X520.

Fig. 9.—African child.
Fig. 10.—African child.
Fig. 11.—American child.
Fig. 12.—American child.
Significant Aspects of Childhood Lymphoma in Africa

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