

Clinical Epidemiology of Leukemia

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IN STUDIES OF LEUKEMOGENESIS, the contribution of epidemiology is greatest when it interacts—with the clinic or the laboratory. This paper reviews recent clinical-epidemiologic developments, with a range of information from single cases to large populations, which have provided some insight into etiologic factors in leukemia.

PATTERNS OF OCCURRENCE

Demographic patterns have suggested leads to the etiology of leukemia. The sharp age peak for leukemia at 3-4 years which occurs among U.S. white children, but not among the U.S. nonwhites or in Japan, appears to be specific for acute lymphocytic leukemia.¹¹ An additional, smaller, peak at adolescence is due to acute myeloid leukemia.⁴⁸ Although the mechanisms underlying these age variations are uncertain, the patterns suggest the influence of host factors: genetic susceptibility in early childhood and hormonal changes in adolescence. The relatively low frequency of leukemia in Japan⁹ and other Oriental countries⁴¹ may be ascribed to the near absence of chronic lymphocytic leukemia. The deficiency may result from a lack of genetic susceptibility, as suggested by a preliminary study of Japanese immigrants to the U.S. who have shown, as yet, no increase in mortality from this disease.³⁶ These descriptive studies support the notion that leukemia is a heterogeneous complex of diseases. Although an environmental leukemogen such as radiation can induce many (but not all) forms of leukemia, the demographic patterns of each cell type of leukemia are sufficiently dissimilar to suggest etiologic differences between them.

A recent downturn in leukemia mortality has been reported for the U.S. white population, especially in young children.²⁷ Whether or not the trend is due to diminished exposure to an environmental leukemogen, such as more cautious use of medical x-rays which followed recognition of the hazards, should be clarified by study of leukemia patterns by cell type in the future. Even a cytologic type of leukemia may consist of etiologically distinct entities, as is suggested by recent studies of chronic myelogenous leukemia which show clinical-epidemiologic differences between patients with and without the Philadelphia chromosome.⁸³

THE ENVIRONMENT

Radiation

Radiation in sufficiently high doses is known to cause chronic myelogenous leukemia and acute leukemia. This evidence has been obtained mainly from the follow-up studies of patients receiving partial-body radiation for treatment

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of ankylosing spondylitis,¹² and survivors of the atomic blasts in Hiroshima and Nagasaki, where 20 years later the rates for acute leukemia are still excessive.³ Among the various groups exposed to radiation, the highest risk of leukemia has been found among patients with polycythemia vera who have been treated with x-ray, radioactive phosphorus, or both.⁶⁶ Whether or not the frequency of leukemia (16 per cent within 10-15 years) can be ascribed to radiation damage alone⁶⁶ should be clarified by a prospective study in progress.⁸⁰ The exceptional risk of leukemia may result from the interaction of radiation with a disease which is intrinsically susceptible, on the basis of its overproliferative character or its recently described chromosomal aneuploid.⁷ The mechanism may be similar to the process by which chronic myelogenous leukemia "converts" to acute leukemia.⁵⁴

Preconceptional diagnostic irradiation of parents was reported recently to increase the risk of leukemia among children conceived after exposure; a retrospective case-control study of 319 children showed a relative risk of 1.6 and 1.3, respectively, following radiation-exposure of future mothers or fathers.³³ In contrast, a prospective study of 17,700 children by the Atomic Bomb Casualty Commission (ABCC) showed no increase in leukemia after much heavier exposure of their parents to preconceptional radiation.⁷⁷ Furthermore, there was no excess of chromosomal abnormalities—an index of radiation effect—among children conceived at various intervals since the mothers or fathers were exposed to the atomic blast.¹ In a similar manner, retrospective studies have shown a relation between maternal preconceptional irradiation and Down's syndrome^{77, 86} or other trisomies⁸⁶ in the offspring, whereas no such excesses were observed in the ABCC follow-up.⁷⁷ The lack of consistency and specificity of effect suggests that the association between preconceptional radiation and leukemia is not causal, but results from some aspect of the underlying state which required radiologic examination.^{58, 61}

Several retrospective and prospective studies have indicated that diagnostic radiation during pregnancy may as much as double the risk of childhood leukemia.^{33, 50} However, the magnitude of the association is similar to that observed with preconceptional radiation, suggesting the influence of as yet unknown confounding variables. This interpretation is strengthened by the same lack of specificity, since *in utero* exposure is associated with equally increased rates for each childhood neoplasm other than leukemia.⁵⁰

Although a dose-response relation is characteristic of radiogenic leukemia,⁵⁸ two recent studies suggest a paradoxical occurrence under certain circumstances. Whereas an excess of leukemia was found in a limited sample of women receiving castrating doses of pelvic irradiation for metropathia hemorrhagica,¹⁷ no increase in risk was observed among women who received much larger dose of radiation for treatment of cervical cancer.⁴² These findings, if confirmed, suggest that under conditions of intense localized irradiation, the marrow cells may have less capacity for transformation than when more lightly exposed. Further clarification awaits completion of a follow-up study of a large sample of women who received ovarian irradiation for benign gynecologic disease.⁶⁴

Chemicals

A follow-up survey of 124 persons with bone-marrow depression attributed to chloramphenicol revealed the development of leukemia in three instances, although only one had characteristics indicative of a causal relation between drug exposure and leukemia." Another patient in this study group, however, subsequently developed leukemia and was reported separately.¹⁰ Other case reports linking chloramphenicol toxicity to leukemias and to chromosomal aberrations^{8,71} have enhanced the possibility that this drug has leukemogenic potential. Since radiation,⁵ benzene,⁸³ and chloramphenicol have the capacity to depress the bone-marrow and damage chromosomes, other agents with these characteristics should be evaluated for leukemogenic activity.

Viruses

Despite the discovery that several leukemias in laboratory animals are virally induced, there is as yet no epidemiologic substantiation of the hypothesis that human leukemia is transmitted by infectious agents.^{26,59,63} Evidence is lacking to incriminate "vertical" transmission of an agent (from one generation to the next), as demonstrated for murine leukemia; for example, no excess of leukemia was found among offspring of mothers who were leukemic during pregnancy,^{21,55} and the breast-feeding experience of leukemic children was similar to that of a control group.⁶⁵ "Horizontal" (contagious) spread of leukemia has been suggested by anecdotal reports of "clusters," but most statistical studies which detect epidemicity of a low order have implicated random variation as the basis for the clustering of cases—with respect to the time and place in which the leukemia developed or the patient was born.^{23,26,31} Although the use of one technic in different populations has indicated weak clustering of leukemia among young children within variable time and space distances,³⁵ the effect may be due to a methodologic bias or demographic shifts.^{32,37} Furthermore, the risk of leukemia is not increased in children receiving neonatal exchange transfusions,^{14,58} in spouses of leukemic patients,³⁰ in the masters of leukemic dogs,³² in certain seasons²⁰ or in other situations that might reflect the infectious spread of disease.

A particular agent recently incriminated in childhood leukemia is simian virus 40, which is oncogenic in laboratory animals and was contained in many early lots of polio vaccine.²⁴ A report from Australia indicated that leukemic children received significantly more polio vaccine (presumed to contain SV-40) than did a control pup, with no such difference in other immunizations.⁴⁵ However, comparison of the leukemia mortality experience of 3 groups of 6- to 8-year-old children receiving polio vaccine during the U.S. mass vaccination program of 1955 showed no differences according to the dose-level of SV-40 which contaminated certain lots.²⁴ Furthermore, among a group of newborns (the age of maximum susceptibility to oncogenic agents) that inadvertently received batches of polio vaccine containing high doses of SV-40, none have

of leukemia or observations).

The recent discovery of antibodies to the E. coli virus caused speculation that a hematopoietic neoplasm might have a possible relation between military veterans who served in the Korean War. This survey will also assess the possibility of hepatitis, a disease suspected of diminishing the risk of leukemia.

Since the study of leukemia is progressing in detecting the laboratory research characteristics conferred by the virus.

Heritable Disorders

The twentyfold or more increase in the risk of leukemia in children with Down's syndrome,³⁸ in which the risk results from meiotic nondisjunction of chromosomes (aneuploidia), is a clear indication of a causal relation of leukemia. In many of these disorders, the risk of leukemia is especially great during the first 5 years of life, and conditions should be established to permit the diagnosis of leukemia in affected children. Hereditary forms of aneuploidy, such as Down's and D-trisomy syndrome, are associated with leukemia, although follow-up studies have not confirmed this association. Since a cytogenetic study of leukemia in yielding antecedent conditions and skin cells of 25 children found 3 with aneuploidy, an elongated Y. Of these, 2 had abnormalities in 3 chromosomes and 2 of 15 children had leukemia.⁵⁴ and 2 of 15

Susceptibility to leukemia is an autosomal recessive trait in an autosomal recessive trait, and rearrangement of chromosomes in Bloom's syndrome is a rare and unusual factor in the development of leukemia as myelogenous.⁷⁵ A

rs indicate that exposure is less convincing. A follow-up survey of chloramphenicol resistance, although only one had exposure and subsequently developed leukemia, linking chloramphenicol resistance^{6,71} have enormous potential. Since the capacity to depress the immune system with these characteris-

died of leukemia or other cancers in the first eight years of life (unpublished observations).

The recent discovery that patients with infectious mononucleosis acquired antibodies to the EB virus derived from Burkitt-lymphoma cell lines¹⁸ has caused speculation that this virus induces both infectious mononucleosis and hematopoietic neoplasia. Epidemiologic studies are in progress to evaluate a possible relation between the two diseases, including a follow-up survey of military veterans who contracted mononucleosis during World War II.⁵⁹ This survey will also assess the relation of leukemia and other cancers to infectious hepatitis, a disease which also harbors the EB virus," and which has been suspected of diminishing the risk of cancer.⁵⁹

Since the study of leukemia clusters or "viral-like" patterns has made little progress in detecting leukemogenic agents, more promising as subjects for laboratory research would appear to be those groups of individuals whose host characteristics confer an exceptional risk of leukemia.

THE HOST

Heritable Disorders

ry animals are virally induced. The hypothesis that evidence is lacking in one generation to the next, no excess of leukemia in children was observed (spontaneous) spread of leukemia, but most statistical studies indicated random variation with respect to the time and place of birth.^{23,26,31} Although, it has indicated weak association with time and space, no bias or demographic differences in children relative to leukemia patients.¹⁰⁰ or in other situations

The twentyfold or greater increase of leukemia among persons with Down's syndrome⁶⁰ in which the characteristic chromosomal defect (trisomy 21) results from meiotic nondisjunction prior to conception, suggests that extra chromosomes (aneuploidy) play a role in leukemogenesis. More tenuous is the relation of leukemia to other congenital chromosomal defects, perhaps since many of these disorders are rare, highly lethal, and/or poorly recognized. Since the risk of leukemia in mongolism is increased at all ages and appears especially great during neonatal life,⁶⁴ the frequency of leukemia in other conditions should be estimated more precisely when techniques are developed to permit the diagnosis of such defects early in life and improve the survival of affected children. However, compilation of case reports²⁶ suggests that other forms of aneuploidy—Klinefelter's syndrome (XXY or variants) in 4 patients and D-trisomy syndrome in 2 newborn infants^{74,92}—are related to leukemia, although follow-up study of more affected children is needed to establish an association. Since aneuploidy may occur in phenotypically normal persons, cytogenetic study of leukemic patients in remission might be more productive in yielding antecedent defects. In such a study based on examination of blood and skin cells of 25 leukemic children without somatic anomalies, Borges et al.⁷ found 3 with aneuploidy (XXY, probably XYY, and F-trisomy) and one with an elongated Y. Other investigators have reported prezygotic chromosomal abnormalities in 3 of 52 persons of all ages with chronic myelogenous leukemia,⁹⁰ and 2 of 15 patients with acute leukemia.⁶⁷

Susceptibility to leukemia is strongly suggested in 3 diseases. all inherited in an autosomal recessive pattern which show increased chromosomal breakage and rearrangement on cell culture.⁶⁸ Among 23 patients reported with Bloom's syndrome (featuring photo-sensitive telangiectatic facial rash, dwarfism and unusual facies), 3 developed acute leukemia, described in 2 instances as myelogenous.⁷³ Acute leukemia of the monocytic type has been documented

1 leukemia is simian-like as contained in many studies indicated that leukemic cells need to contain SV-40) after immunizations.⁴³ One of 3 groups of 6- to 10-year-old children in the U.S. mass vaccination program received a dose-level of SV-40 (a group of newborns) that inadvertently received SV-40, none have

in 3 patients with Fanconi's syndrome of aplastic anemia and multiple anomalies.^{6,32} Ataxia-telangiectasia, which has an immune-deficiency state and appears to predispose to lymphoma (see below), has been reported in 3 children with acute leukemia,^{37,39} including 2 sibs with the lymphatic type.³⁹ Despite the small number of cases, the type-specific nature of the acute leukemia in each condition would appear to extend the evidence for heterogeneity in leukemia and suggests distinct host-related pathogenic mechanisms for various forms of acute leukemia.

Whereas congenital cytogenetic defects predispose to various leukemias, review²⁶ of case studies suggests that lymphoma occurs disproportionately among the genetic syndromes associated with immune deficiency, such as ataxia-telangiectasia, Wiskott-Aldrich syndrome, and sex-linked agammaglobulinemia. Epidemiologic support for the relation of immune deficiency to lymphoma was provided recently by a study of the British Medical Research Council; among 176 persons with hypogammaglobulinemia (all presumed to be genetically-induced) followed over variable periods of time, 6 subsequently developed lymphoreticular neoplasms.⁵⁵

It remains to be determined whether or not other congenital disorders, not associated with chromosomal or immunologic defects, are related to an increased risk of leukemia. One possibility would be osteogenesis imperfecta, which has been reported with acute lymphatic leukemia in 2 sibs.²⁹ Individual case reports of childhood leukemia with achondroplasia,²⁵ Marfan's syndrome,⁷⁰ Klippel-Feil syndrome,⁷⁹ and a variant of the Ellis-van Creveld syndrome,⁵⁷ suggests a general relation between leukemia and genetically-determined diseases of the skeletal system. Such a relation, if established, would extend the spectrum of hematologic disorders which have been observed with congenital syndromes involving skeletal abnormality.¹⁵

Other Evidence of a Genetic Influence

There is increasing evidence, beyond the concurrence of leukemia with heritable disorders, that genetic factors may influence leukemogenesis. In childhood, the contribution of inheritance may be estimated by the concordance rate of 20 per cent among identical twins, while no concordance occurred for fraternal twins.⁵¹ Recently confirmed,⁶² this finding suggests that leukemogenic mechanisms may be clarified by laboratory study of unaffected identical twins of children diagnosed with leukemia. Genetic factors probably account also for the fourfold increased risk of leukemia among sibs of leukemic children,⁶² although the influence of environmental factors cannot be excluded. Recent case reports include families in which 3 or more young sibs developed acute lymphocytic leukemia,^{34,45} 2 sets of infant sibs had chronic myelogenous leukemia in the absence of the Philadelphia chromosome,⁴⁰ and 3 children related as cousins showed a myeloproliferative disorder resembling myelogenous leukemia.⁶⁸ Familial aggregation of leukemia among adults, while awaiting epidemiologic substantiation, is strongly suggested by case studies of families with a high frequency of specific forms of leukemia, most often the chronic lymphocytic variety.¹⁹

CLINICAL EPIDEMIOLOGY

The recessive inheritance of acute leukemia and lymphomas, these neoplasms. This possibility is consistent with the high percentage of consanguinity in 40 per cent of acute childhood leukemia and chronic lymphocytic leukemia.

High Risk Disorders

A number of congenital disorders, such as leukemia or lymphoma with the congenital defects, such as cythemia vera with phosphorus admixtures revealed a high risk of treatment with radiation. It has been found to carry a high risk of reports suggest that anemia.¹³ Chromosomal defects, such as refractory anemias,¹⁰

Lymphoreticular neoplasms, "acquired" disorders, such as hyperreactivity. "Acquired" disorders, such as leukemia show a high risk with adult celiac disease (including 10 with lymphoma).³⁸ A study of lymphoma cell sarcoma in one.⁵¹ Factors should clarify the role of hyperthyroidism drawn attention to the role of neoplasms appear in the pathogenesis and follow-up of suppressive therapy, transplantation, celiac disease occur in leukemia. Mechanisms. This is consistent with a high risk of disease.

Coexistent Neoplasms

In a prospective study, a significant association was observed between leukemia and other neoplasms.

multiple anomaly state and reported in 3 children of lymphatic type.³⁹ The acute leukemia heterogeneity and mechanisms for vari-

ous leukemias, regionally among such as ataxia-telangiectasia, lymphoma was Council; among be genetically-ly developed

disorders, not related to an in-esis imperfecta, bs.²⁹ Individual in's syndrome,⁷⁰ syndrome,⁷⁷ sug-germined diseases extend the spec-congenital syn-

leukemia with hemogenesis. In by the concord-ance occurred ggests that leu-ty of unaffected factors probably sibs of leukemic not be excluded. sibs developed nic myelogenous and 9 children embling myelo-g adults, while y case studies of most often the

The recessively inherited diseases (previously noted) which predispose to leukemia and lymphoma suggest that, even in the absence of genetic syndromes, these neoplasms may be subject to the influence of recessive genes. This possibility is supported by a recent study from Japan, where about 4 per cent of marriages occur among first cousins,⁴³ which revealed parental consanguinity in 4 of 7 sib pairs with leukemia at various ages.⁴⁷ In this country, consanguinity has been reported infrequently in case studies—? aggregations of acute childhood leukemia involving 3 or more sibs,^{44,78} and a cluster of chronic lymphocytic leukemia in 3 adult sibs (unpublished observation).

High Risk Disorders of Adults

A number of conditions of an "acquired" nature appear to predispose to leukemia or lymphoma, although putative mechanisms are more obscure than with the congenital disorders. In contrast to the epidemiologic survey of polycythemia vera which ascribed a heightened risk of leukemia to the radioactive phosphorus administered as therapy,⁸⁰ a follow-up study of hyperthyroid patients revealed a 50 per cent increase of all forms of leukemia regardless of treatment with radioactive iodine.⁷² In addition, pernicious anemia has been found to carry a small increased risk of myelogenous leukemia,⁷ and case reports suggest that leukemia can evolve from certain forms of refracton anemia.¹³ Chromosomal aberrations observed in the megaloblastic⁴ and refractory anemias¹² may play a role in the increased susceptibility to leukemia.

Lymphoreticular neoplasms also appear to occur excessively in particular "acquired" disorders characterized by immunologic deficiency and/or lymphoid hyperreactivity. "Acquired" as well as congenital forms of hypogammaglobulinemia show a high risk of such tumors.⁵⁵ In addition, among 202 patients with adult celiac disease or idiopathic steatorrhea, 14 developed lymphomas (including 10 with reticulum cell sarcoma involving the gastrointestinal tract).³⁸ A study of 58 patients followed with Sjögren's syndrome revealed that reticulum cell sarcoma occurred in 3 cases, and Waldenström's macroglobulinemia in one.⁵¹ Further reports on the follow-up survey of hyperthyroid patients should clarify the suggestion derived from a case series that long-standing hyperthyroidism predisposes to lymphoma.⁸⁷ Finally, case reports have drawn attention to two environmentally-triggered conditions. Lymphoreticular neoplasms appear to occur excessively in hydantoin-induced lymphadenopathy²⁸ and following renal homotransplantation associated with immunosuppressive therapy.¹⁸ The unusual proportion of reticulum cell sarcomas after transplantation, celiac disease and Sjögren's syndrome suggests that, as may occur in leukemia, certain cell types of lymphoma have distinct etiopathogenic mechanisms. This concept is relevant even when the neoplasm is unassociated with a high risk disorder.

Coexistent Neoplasms

In a prospective study of patients with leukemia and lymphoma, Berg² observed a significant increase in the risk of further cancers. By far the largest excess occurred for cancers of the skin which had a conservatively-estimated

risk of ninefold after myeloid leukemia, fourfold after lymphatic leukemia, and twofold after the lymphomas. Of related interest are recent case reports of mucocutaneous carcinomas occurring in the leukemia-prone conditions: Bloom's syndrome,⁷³ Fanconi's syndrome,⁸⁰ and ataxia-telangiectasia.⁸¹ The apparent predisposition to skin cancer or leukemia in the inherited disorders indicates that, in the absence of the syndromes, the concurrence of such neoplasms in one individual may represent a genetically-determined response to an oncogenic agent. Susceptibility to skin cancer in the genetic syndromes suggests an *in vivo* counterpart to the observation that cultured skin fibroblasts from persons with Fanconi's syndrome or autosomal trisomy are exceptionally sensitive to SV-40 transformation.⁶⁵

SUMMARY

Heterogeneity in the etiopathogenesis of leukemia appears to be reflected in dissimilarities of distribution by cell type in the general population, as well as in several groups at unusually high risk of the neoplasm.

Radiation in sufficient dose is known to cause human leukemia. There is some question, however, about the small increase in risk during childhood following very low doses of preconceptional or intrauterine radiation. The possibility exists that the underlying disorder for which diagnostic radiation was prescribed is directly related to the neoplasm, with radiation merely an indicator of the host abnormality. Other influences may enhance the leukemogenic potential of radiation, as suggested by the very high rate of leukemia among patients irradiated for polycythemia vera. Benzene is the only chemical agent strongly suggested to be leukemogenic on the basis of striking occupational clusters, although recent suspicion has been directed to chloramphenicol.

Despite the discovery that viruses can cause leukemia in laboratory animals, convincing evidence of a viral influence in human leukemia has not been achieved by the epidemiologic technics designed to detect an infectious spread. However, this influence would have gone unnoticed if the agents are: (1) not transmitted in the manner of other human pathogenic viruses, (2) too evanescent, or (3) so ubiquitous that only nonviral "trigger" mechanisms are detectable. Since intensive investigation of leukemia clusters has made little progress so far in identifying leukemogenic agents, an apparently more encouraging approach for laboratory research would utilize groups of individuals at unusually high risk of leukemia.

Evidence is accumulating that certain inborn disorders associated with cytogenetic defects carry an increased risk of leukemia, whereas inherited syndromes of immune deficiency predispose primarily to the lymphomas. Genetic factors are further indicated by familial patterns in leukemia, some of which implicate the influence of recessive genes. Chromosomal and immunologic defects also accompany or mediate the heightened risk of leukemia and lymphoma among certain idiopathic or environmentally-induced conditions. The special influence of abnormal immunologic mechanisms in the origin of reticulum cell sarcoma is suggested by the high frequency of this cell type in Sjögren's syndrome, in celiac disease, and following immunosuppression for renal homotransplantation.

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after lymphatic leukemia, and most are recent case reports of leukemia-prone conditions: ataxia-telangiectasia.⁶⁰ The data in the inherited disorders of the concurrence of such neoplasms suggest a genetically determined response to a factor in the genetic syndromes in which cultured skin fibroblasts with normal trisomy are exceptionally

leukemia appears to be reflected in the general population, as well as in the bone marrow.

In the human leukemia. There is a risk during childhood following in utero radiation. The possibility of diagnostic radiation was with radiation merely an increase may enhance the leukemogenicity. The very high rate of leukemia in benzene is the only chemical agent, the basis of striking occupational exposure directed to chloramphenicol leukemia in laboratory animals. Human leukemia has not been shown to detect an infectious spread. It is suggested if the agents are: (1) not oncogenic viruses, (2) too evanescent. "trigger" mechanisms are demonstrated in leukemia clusters has made little progress, an apparently more useful approach would utilize groups of individuals

disorders associated with leukemia, whereas inherited syndromes are similar to the lymphomas. Genetic studies in leukemia, some of which are chromosomal and immunologic in origin, suggest a risk of leukemia and lymphoma in environmentally-induced conditions. The mechanisms in the origin of reticulocytopenia of this cell type in leukemia following immunosuppression for

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Cytochemistry

THE APPLICATION of defined special microscopy provides metabolic activity in populations. Early of glycogen and re technique, and of in applicability to he ential diagnosis a group. These met for alkaline phosph reliable in significance. The contribution of original publication in recent years,^{9,10} detail here, but lymphoma that die be Hamlet without the well-established normal hemic cells which help in the and contribute to . If these 4 cytochemical service, there are enzymes, that may character of neoplastic evidence in differential phatase,³⁰ aryl sulfatases,^{13,27} aminoglycosidases, and other enzymes. Brief reactions are given formation generally beyond the research hemic cell enzyme can hardly be discussed. modifications of many microscopic use has potential advantages at molecular level in . Cytochemical procedures; they demonstrate

From the Department of