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IS HODGKIN'S DISEASE AN INFECTIOUS DISEASE?

Nedjat Izadian*

ABSTRACT

The exact cause or causes of Hodgkin's disease have not yet been determined. The etiology of the disease suggests, but has not verified, a possible immunological and/or viral relationship. The article reviews the literature on the epidemiology and etiology of Hodgkin's disease from 1955 to the present. The author presents several clinical phenomena that are commonly associated with Hodgkin's disease and which may be useful as diagnostic tools in cases of suspected Hodgkin's disease or with suspicious pathology. The author concludes by suggesting possible areas for future research.

INTRODUCTION

The etiology of Hodgkin's disease (HD) suggests an infectious process, in view of the frequent association of cervical lymphadenopathy with fever, perspiration and weight loss. Viruses have received the greatest attention in studies. Since 1964, when Epstein detected a herpes-type virus (Epstein-Barr virus, EBV) in cultured cells derived from the lymph node of a patient with Burkitt's lymphoma (BL), a number of studies have attempted to determine the relationship of EBV to the etiology of Burkitt's lymphoma.

Burkitt's lymphoma is of particular interest because of its unusual epidemiologic features (Burkitt, 1963; Wright, 1967) which include time clustering and high antibody titers against EBV (Henle, 1966, 1970; Klein, 1967).

The possibility of case clustering in HD (Kryscio, 1963; Peto,

* Department of Pathology, University of Teheran, Teheran, Iran.

1973), was enhanced by observations of Vianna, et al (1971, 1972), who noted that HD was "being transmitted" in a high proportion of cases, either directly from patient to patient or indirectly via a single carrier. It is obvious that viral infections have been implicated in the development of cancer. At this point, the most important epidemiological question about the nature of HD is whether the data, including high anti-body titers against specific viral antigenes, time-space clustering and familial studies, are indicative of and consistent with person-to-person transmission of the disease.

EPIDEMIOLOGICAL DATA

Space-Time Clustering

Shimkin (1955) analyzed the mortality rate from HD in the United States for the period of 1921-1951. The death rate rose from 6.9 per million in 1921 to 17.0 per million in 1951.

In his epidemiologic studies of HD, MacMahon (1966) indicated the following entities for HD:

- HD varies with age at clinical onset.
- There are three distinguishable age periods (see Table I).
- HD has a characteristically bimodal age distribution (Fig. 1)
- HD patients include at least three subgroups, each of whose etiology may be quite different (see Table I).
- In young adults, HD presents as a chronic granulomatous inflammation, but as a neoplasm in adults over age 50.

Bimodality by age is also evident in surveys of extensive data from the Danish Cancer Registry (Clemmesen, 1964, 1965; see also Fig. 2), New York State, 1941-60 (Ferber, 1962) and the U.S. Army, 1941-46 (Cohen, 1964), and appears, therefore, to be a constant feature of Hodgkin's disease. Approportionate age groups (see Fig. 1 and Fig. 2 and Table I) would seem to be:

- 0—14, prior to the first mode.
- 15—34, the first mode.
- 35—49, intermediate between the first and second modes.
- 50 and over, the second mode.

One of the most important studies of time-space clustering in HD was done by Vianna (1972). He analyzed all cases of HD reported in Albany County, New York State, between 1950 and 1970, and compared the reported increase of cases in Albany County with those of the other 56 counties of upstate New York (excluding the metropolitan

area of New York City.) He found the incidence rate of HD to be around 2.5 per million per year for the period, 1950—70, for the other 56 counties whereas Albany County showed the same incidence rate for the years, 1950—62, but an increased incidence rate in 1953 which remained high until 1959 and then fell below average. Thus, Albany County showed an obvious, fluctuating incidence rate. Further investigation indicated 34 cases of lymphoma and 31 cases of HD, linked by direct or indirect contact over a 20-year period (1959—70) from a single high school in upstate New York. This period of high incidence was followed by an apparently reciprocal period, when the incidence of HD fell below average. On the basis of these observations Vianna suggested that the pattern of Hodgkin's disease occurrence was similar to that of an infectious disease.

In 1974, Vianna, et al. investigated the death rate of teaching hospital physicians in upstate New York from 1960 through 1972. They compared this mortality rate with the upstate New York mortality rate of the earlier study and found a rate of 6.9 deaths per million per year for physicians, against a rate of 3.83 deaths per million per year for upstate New York (excluding the metropolitan area of New York City) for the same period. The differences between the two rates were statistically significant (P less than 0.01), with a relative risk of 1.8 for physicians.

Cridland (1961) has reported a seasonal trend for the onset of HD, with a peak in December and January. Cridland hypothesized that upper respiratory infections might be attributed to swollen cervical glands, but found only 10% of the patients to have such infections. Seasonal variation in onset of symptoms has also been noted in leukemia (Lee, et al., 1963, 1965).

On the other hand, Alderson (1971) analyzed the data of 737 HD patients in the Manchester Regional Hospital area. Using the "Knox method", David (1966), for time-space interaction, he found a bimodal distribution of incidence by age, with a high incidence for the age group 45—49. There was evidence of seasonal variation for onset, with peaks of patients first presenting at the hospital in the spring. There was no evidence of time-space clustering in the total data for critical distances up to 12 km and for time differences up to one year, but a year-by-year plot did show evidence of clustering among patients in the age group 15—44, for the years 1963 and 1964.

Kryscio (1973) classified 1, 633 Hodgkin's disease cases by town, residence and year of diagnosis among Connecticut residents during the period 1940—69. He found some clustering. Using the Knox method, he could show no evidence of HD clustering for that area or period of time. These studies show little or not support for the infectious etiology theory, as measured by time-space clustering.

Smith, et al. (1974) investigated a case-control, time-space distribution study of contacts of the 206 HD patients at onset. All patients in the study were under 40 years of age. All had been diagnosed in the Oxford Regional Hospital Board area between 1962 and 1971. Smith found clustering in the 129 pairs of patients who lived within 5 km of each other, with average onset differentials of 403 days. However, when he applied the Knox method, Smith found no evidence of clustering.

Viruses in Hodgkin's Disease

Epstein (1964a, 1964b) first described the technique for growing lymphoma cells in suspension cultures. Many cell lines have since been established. Several of these cultured lines, including some cell lines from normal individuals carry a herpes-like virus (Epstein, 1964b; Stewart, et al., 1965).

Herpes viruses produce a great number of diseases in many animals and humans. Although these viruses share similar morphological and biological characteristics, each herpes virus is serologically and biologically distinct. A number of different viruses of the herpes group are known to infect man. Two of these viruses, herpes virus Hominis (VH) and the Epstein-Barr virus (EPV), have been incriminated as possible etiologic agents in human malignancy. Two separate strains of HVH have been identified according to their different serologic and biologic properties (Plummer, 1970). The type-2 strain is recovered from genital sites and is responsible for over 95% of herpetic genital infections (Nahmias, et al., 1969). This virus has been associated with all stages of carcinoma of the cervix (Nahmias, et al., 1970), and acquisition of antibody to this virus appears to precede the earliest neoplastic changes in patients who subsequently develop *in situ* carcinoma of the uterine cervix.

These findings and many other studies on animals (Goodheart, 1970; Melendeg, 1969; Nahmias, et al., 1969) raise the question of the possible role of HVH in various other human neoplastic diseases.

In 1969, Stewart described a long-term culture of a malignant lymphoma cell line developed from a lymph node specimen taken from a 34-year-old male with HD. Electron microscopy examination of the line showed a herpes-like virus.

Catalano, et al. (1972) did a case-control study of sera from 40 patients with HD and 20 patients with nasopharyngeal carcinoma (NPC). He found that 27% of the 40 patients gave evidence of a prior infection with the type-2 strain of HVH, compared with 10% of sera controls. The differences were borderline significant (P was less than 0.10).

In a case-control study using immunofluorescence technique, Langenhuysen (1974) measured the antibody levels against both EBV

and cytomegalovirus (CMV) in the sera of 25 previously untreated HD patients and in the sera of an age-and-sex-matched control group. They found significant differences in the titers of the patient and control groups. The disseminated form of anti-CMV antibody was significantly elevated.

Hirshaut, et al. (1974) analyzed 36 specimens of HD collected from patients admitted to the Clinical Center of the National Institute of Health in New York. Under electron microscopy, they found evidence of C-type particles in the tissues of 35% of the patients. Positive specimens were obtained from patients with both local (Stages I and II) and widespread (Stages III and IV) disease patterns. Specimens from untreated patients were more likely to contain particles resembling the C-type virus than tissues from treated patients.

Hirshaut, et al. (1974) also analyzed the plasma of patients by an indirect immunofluorescence technique. Antibody to herpes-like virus (HLV) was detected. Sixteen percent of the patients had elevated antibody titers, compared with nine percent of the control group.

In 1975, Gotlieb-Stematsky, et al., compared the sera of 71 leukemia patients and 67 HD patients with that of 186 healthy controls from the Tel Aviv area. An indirect immunofluorescence technique was used to determine antibodies to EB viral antigen. They found a higher level of antibodies to the vital capsid antigen in both leukemia and (particularly) HD patients than in the healthy control group. There were significantly higher titers among Jewish patients of Asian-African origin, compared with those of Jewish patients of European origin, and of Arab patients.

Immunity Aspect in Hodgkin's Disease

Based on clinical and laboratory studies of HD, two immunity systems must be considered: one based on the synthesis and secretion of immunoglobulins, and the other involved in cell hypersensitivity. The former system involves B lymphocytes which develop along a separate line of differentiation from the T cell (a thymus-dependent population). It is possible to identify the cells (T or B cells) of each population by studying certain surface isoantigenic markers. However two questions are central to this point: (1) what cell is monoclonally deviated and expended in HD? and (2) what is the actual basis of the T-cell immunodeficiency in this disease?

Cellular immunity is impaired in many HD patients. Therefore, lymphocutes play an important role in this aspect. The lymphoid cell population in the peripheral blood of HD patients is identical with that found under conditions of known "antigenic challenge in man" (Crowther, et al., 1969).

In 1973, Hamilton, et al., attempted to determine the significance

of the "antigenic challenge" in relation to the activity, the stage, the histology and the prognosis of HD patients. They investigated the presence of cutaneous, delayed hypersensitivity reaction and mixed lymphocyte reactions. They found that the changes of lymphocytes in HD were related only to the activity, but not to the other factors.

Evidence for a tumor-associated antigen in HD was reported by Order, et al., in 1971 and by Peckham, et al., in 1973. They found that some cells in HD do have new antigens, although their information did not indicate that the antigens were tumor specific. (For that reason, they called them "tumor associated".

Bjorkholm, et al. (1975), investigating immunodeficiency and prognosis in HD, analyzed blood lymphocytes from 33 untreated HD patients, and found immunological abnormalities which reflected a T-lymphocyte deficiency (significant in advanced cases) and impairment in DNA synthesis.

Lymphocytes in the peripheral blood of humans have been shown to be a heterogeneous population, composed of bone-marrow-derived (B) lymphocytes (Bursa equivalent), Bobrove, et al., 1975) and thymus-derived (T) lymphocytes. B lymphocytes bear surface immunoglobulin (Ig) and mediated humoral immune responses. T lymphocytes have specific surface antigens which react with antihuman thymocyte sera absorbed with B cells (Unanne, et al., 1972; Smith, et al., 1973) and spontaneously combine with sheep erythrocytes to form "rosettes".

Bobrove, et al. (1973) analyzed peripheral blood T and B lymphocytes of 42 HD patients to determine whether the defect in cell-mediated immunity in patients with HD was related to a quantitative and/or a functional deficit of T lymphocytes in the peripheral blood. They found that the percentage and total number of T cells of blood was similar, both in patients and in normal subjects. The percentage of T lymphocytes, determined by the E-Rosette assay* and by the Cytotoxicity assay**, were similar to that of normal subjects, except that determination by E-Rosette assay was significantly lower than by Cytotoxicity assay in HD patients.

A decreased response to phytohemagglutinin (PHA) stimulation in these HD patients was related to the decline in E-Rosette formation. From these findings, Bobrove, et al., concluded that T lymphocytes in the peripheal blood of the HD patients were not diminished, but that a proportion of them had altered their surface interactions which might have resulted in impairment of their immunologic function.

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* Normal T lymphocytes plus sheep erythrocytes gives E-Rosettes.

** Normal T lymphocytes plus complement-dependent cytotoxicity (a specific anticell serum) will kill 100% of the T lymphocytes.

Tonsillectomy History in HD Patients

A relationship has been suggested between tonsillitis leading to tonsillectomy and the probability of subsequent onset of HD (Miller, 1966; Gross, 1966). Further investigation of this relationship elicited the finding of a high incidence of prior tonsillectomy in patients with HD (Vianna, et al., 1971). In several reports, such contacts were speculated to be potential carriers of transmissable etiologic agent(s). Vianna, et al. (1971) suggested that intact tonsils might provide a barrier to the introduction of disease in the individual, while permitting a carrier stage.

In 1972, Johnson, et al., analyzed the history of 174 HD patients and found a history of tonsillectomy in 52% of these patients. The percentage of tonsillectomy history decreased in patients under the age of 16. There was no relationship between tonsillectomy history and the clinical features of HD, nor did these findings support the hypothesis that prior tonsillectomy increased susceptibility to HD by "removal of a lymphoid barrier".

When Vianna, et al. (1971) compared 135 young adult HD patients with their 315 siblings and 78 mates who had had tonsillectomies, they found a risk of 1.4 for siblings and 3.1 for mates. The ratio was consistent with the increased risk of HD for people who had had tonsillectomy, but it was not statistically significant.

(Married patients had a higher tonsillectomy rate (75%) than unmarried (47%).)

Familial Studies in Hodgkin's Disease

Several familial studies of HD have been performed, and the occurrence of multiple cases of HD in families in recognized (Creagan, et al., 1972; Maldonado, et al., 1972; Fraumeni, 1974; and Klinger, 1973). The pattern of space-time clustering was similar to that in an earlier study (Vianna, et al., 1971).

Dworsky (1974) found clustering in marital partners, heroin addicts and students from a junior high school. Dworsky found that there was some tendency for HD to cluster in families; i.e., an approximately threefold excess risk in first-degree relatives, but it is not clear whether this increased risk represents inherited susceptibility or common exposure to known or unknown environmental carcinogenic influences.

Fraumeni (1974) suggested that clustering in HD implicates transmissible agent(s) as at least one factor in the pathogenesis of the disease. The tendency towards familial aggregation of time of onset, rather than age at onset also indicates that environmental factors may be more important than genetic factors (MacMahon, 1966).

DISCUSSION

In recent years, there has been a dramatic surge of interest in the study of all aspects of Hodgkin's disease. Increased attention is now being paid to the epidemiology, virology and immunology of the disease in the hope that the interrelationship of these three aspects may suggest new and stable hypotheses relating to the etiology of the disease.

Epidemiology

Evidence from various epidemiological studies indicates that HD is chiefly an environmentally determined disorder (MacMahon, 1966) which may be horizontally transmitted under certain circumstances (Vianna, et al., 1972, 1973). Much attention has been focused on HD because it has clinical and pathological features that are similar to those found in infectious disease. The possibility of time-space clustering in HD seems to have been ruled out (Alderson, et al., 1971; Kryscio, et al., 1973; Smith, et al., 1974), although other studies suggest a correlation (Shimkin, 1955; MacMahon, 1966; Vianna, 1972; Vianna, et al., 1971a, 1971b).

Other epidemiological evidence related to the infectious etiology of HD comes from familial studies and studies of the incidence of HD among physicians (Vianna, et al., 1971). Increased risk for HD can be observed in families by looking at the age of onset and histologic type of the neoplasm (Creagan, et al., 1971; Fraumeni, 1974; Maldonado, et al., 1972; Levine, 1974).

Despite the preponderance of such studies, there is still some doubt about the etiological significance of familial aggregation: does it represent inherited susceptibility or common exposure to known or unknown environmental carcinogenic influences? There are a few clues about the possible genetic relationship involved in the development of a neoplasm (Young, et al., 1972; Faguet, 1975). But environmental causation seems more likely than hereditary factors because date of diagnosis of HD in familial studies shows a greater correlation than age at onset.

Virology

Two suggestions related to the viral etiology of HD have recently attracted considerable attention. Vianna's (1971) study suggested that case-contact transmission of the neoplasm might lead to epidemics. Fraumeni indicated that infectious mononucleosis (IM) might be a predisposing factor to HD.

Miller, et al. (1973) reviewed the possible association between IM and HD, but found no evidence for a relationship between clinical IM and HD. Newell, et al.'s (1973) data revealed a relative risk of only 1.4

for the development of HD in those who had had IM, although case-control studies (Newell, et al., 1973) did show an association between IM and malignancy.

EBV has received the greatest attention by far in studies concerned with the causation of human cancer. And considerable circumstantial evidence has been assembled about the possible oncogenicity of EBV in African Burkitt's lymphoma (Epstein, et al., 1964; Burkitt, 1963; Wright, 1967; Henle, et al., 1966; Epstein, et al., 1964a, 1964b; Stewart, et al., 1965), in HD (Stewart, et al., 1969; Langhuysen, et al 1974; Hirshaut, et al., 1974; Catalano, et al., 1972; Gotlieb-Stematsky, et al., 1973) and probably with other lympho-proliferative tumors. The virus exists in close association with lymphoid tumor cells in terms of surface antigens, and the existence of viral particles and antigen have been found by many investigators under culture conditions (Crowther, et al., 1969; Order, et al., 1971, 1972; Bjorkholm, et al., 1975; Bobrove, et al., 1975). Statistically significant elevations of anti-EBV titers have been found in lymphocyte-deficient forms of HD (Johansson, et al., 1970; Langenhuysen, et al., 1974). But whether these observations indicate an etiologic relationship to EBV infection is uncertain.

Immunology

The present focus of study is on the immunologic state of the host. Several investigations support the hypothesis of an immunologic deficiency state in lymphoproliferative tumors, particularly in HD (Order, et al., 1971, 1972; Peckham, et al., 1973; Bobrove, et al., 1975; Unanne, et al., 1971; Smith, et al., 1973; Newell, et al., 1973).

Cellular immunity is impaired in many HD patients, especially in those with widespread disease (Hamilton, et al., 1973). Several studies have demonstrated impaired ability to reject homografts and decreased resistance to infections caused by fungi, viruses and mycobacteria in patients with HD (Bobrove, et al., 1973; Smith, et al., 1973; Order, et al., 1972). Anderson (1974) has shown that the level of lymphocytes in the peripheral blood of HD patients is generally low. Extensive studies of lymphocyte activation by phytohemagglutinin (PHA) indicate the existence of a deficit in cell-mediated immunity in HD patients (Crowther, et al., 1969; Bjorkholm, et al., 1975).

The results gained from such studies should help determine which individuals are at high risk to HD. The risk of malignancies is known to increase in such immunodeficiency diseases as HD, but the distribution by histologic type remains unchanged (Young, et al., 1972). Finally, Young et al. (1972) and Matchett, et al. (1973) have hypothesized that there is an intrinsic, functional lymphocyte abnormality inherent in HD. This abnormality may reflect *in vivo* stimulation of the cells by

Hodgkin's tumor-specific antigens, a pattern which would develop early in the course of the disease. With progression of the disease, this initially subtle impairment becomes more pronounced, leading to progressive immuno-incompetence with loss of immunologic memory and shortened cell survival which is reflected by *in vitro* cell death and *in vivo* cell depletion, with lymphopenia found in most HD patients with advanced disease.

Clinical Observations

Several studies have investigated the immunologic status of patients with HD. Order, et al. (1971) reported finding a "tumor-associated antigen" in HD. Hancock, et al. (1976a, 1976b) investigated the sensitization of HD patients' lymphocytes to splenic tissue, and found that the migration of leucocytes was inhibited in 31 out of 55 patients with HD. Stantoro, et al. (1977) demonstrated the existence of a local immunological reaction (involving spleens) against Reed-Sternberg cells in patients with HD; they also found an increase in T lymphocytes in these spleens. The presence of these phenomena can be a helpful diagnostic tool in cases of suspected HD, or with suspicious pathology.

SUMMARY

This review summarizes the state of knowledge and comments on the possible direction of future work in determining the cause or causes of Hodgkin's disease.

Investigation should continue in exploring the relationship between viral infections and HD. Although the precise role of viruses and other factors in tumor formation cannot yet be defined.

The nature of the tumor-associated antigens known to be present in Hodgkin's disease will resolve the question of the pathogenesis of the disease.

In view of the increasing laboratory work with oncogenic agents, an epidemiologic study of HD is essential, to determine whether horizontal transmission of the disease can occur. If such transmissibility is found, particular high-risk groups such as doctors, nurses and technicians should be followed closely. A registry of exposed people has already been proposed.

TABLE I

Epidemiologic Features of Three Subgroups of Patients with Hodgkin's Disease

Variable	Subgroups distinguished by age at clinical onset		
	0–14 years	15–34 years	50 years and over
Peak age of onset	?	25–29	65–74
Sex ratio (% male)	85%	54%	63%
Race (USA)	?	Negro rates approximately 75% of white rates	Negro rates approximately 75% of white rates
Religion (New York City)	?	No association	Jews higher than Catholics or Protestants (approximately twofold)
Socio-economic status (UK, USA)	?	Associated with high socioeconomic status (approximately twofold)	Associated with high socioeconomic status (approximately twofold)
Secular trend (USA):		Increase (140%)	Increase (110%)
Last 40 years	Decline (65%)	Increase (140%)	Increase (110%)
Last 15 years	Decline (20%)	Slight increase (15%)	Constant
Urban:Rural (Denmark)	Rural higher than urban	No difference	No difference for males. Urban, higher for females (?)
International comparison	Reported very high in some areas (e.g. Peru)	More common in Netherlands (1.8 times), Denmark (1.5 times and 7 other reporting countries than in USA; almost absent in Japan	More common in USA than in any other country reporting mortality; as common in Japan as in some European countries.
Familial concentration	?	Small but definite	?

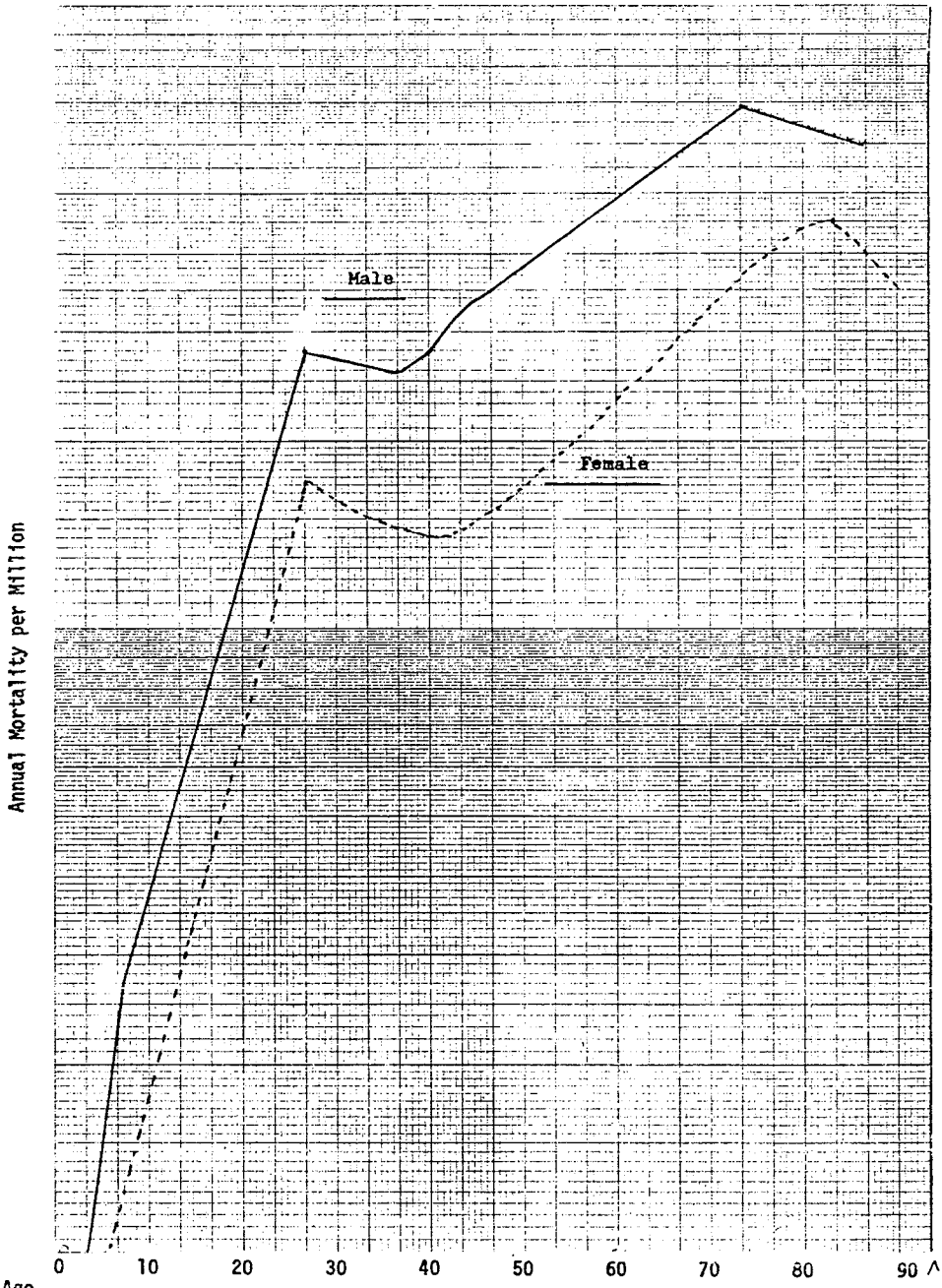

Figure 1. Age-specific mortality rate from HD by sex. United States, 1958-62. (Data from National Center for Health Statistics)

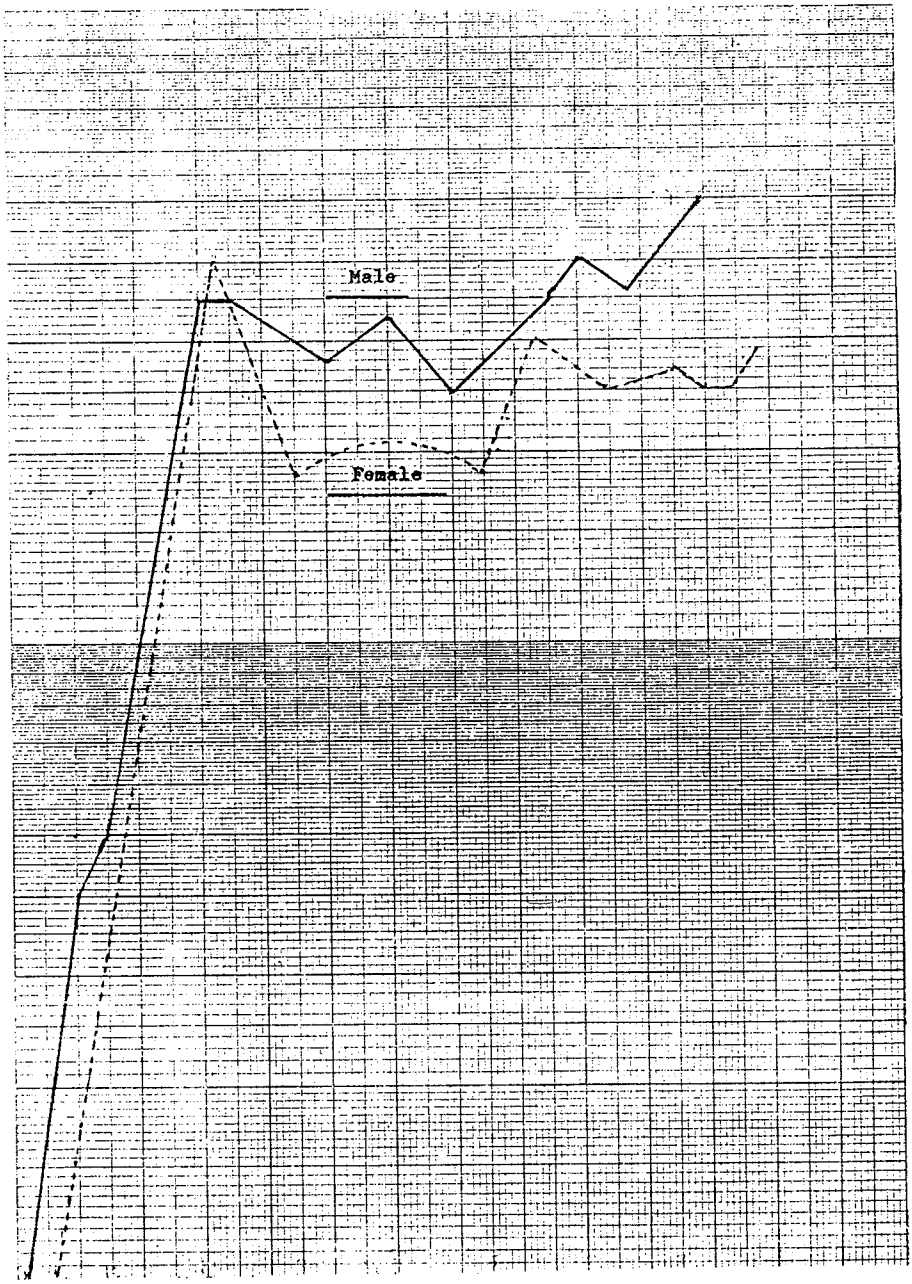

Figure 2. Age-specific incidence rate of HD by sex. Denmark, 1943-57. (Data from Clemmesen)

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