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بالرسالة صفحات
لم ترد بالأصل

ACETYLATOR PHENOTYPE IN LYMPHOMAS

*Thesis Submitted for Partial Fulfillment of
Master Degree in Internal Medicine*

By

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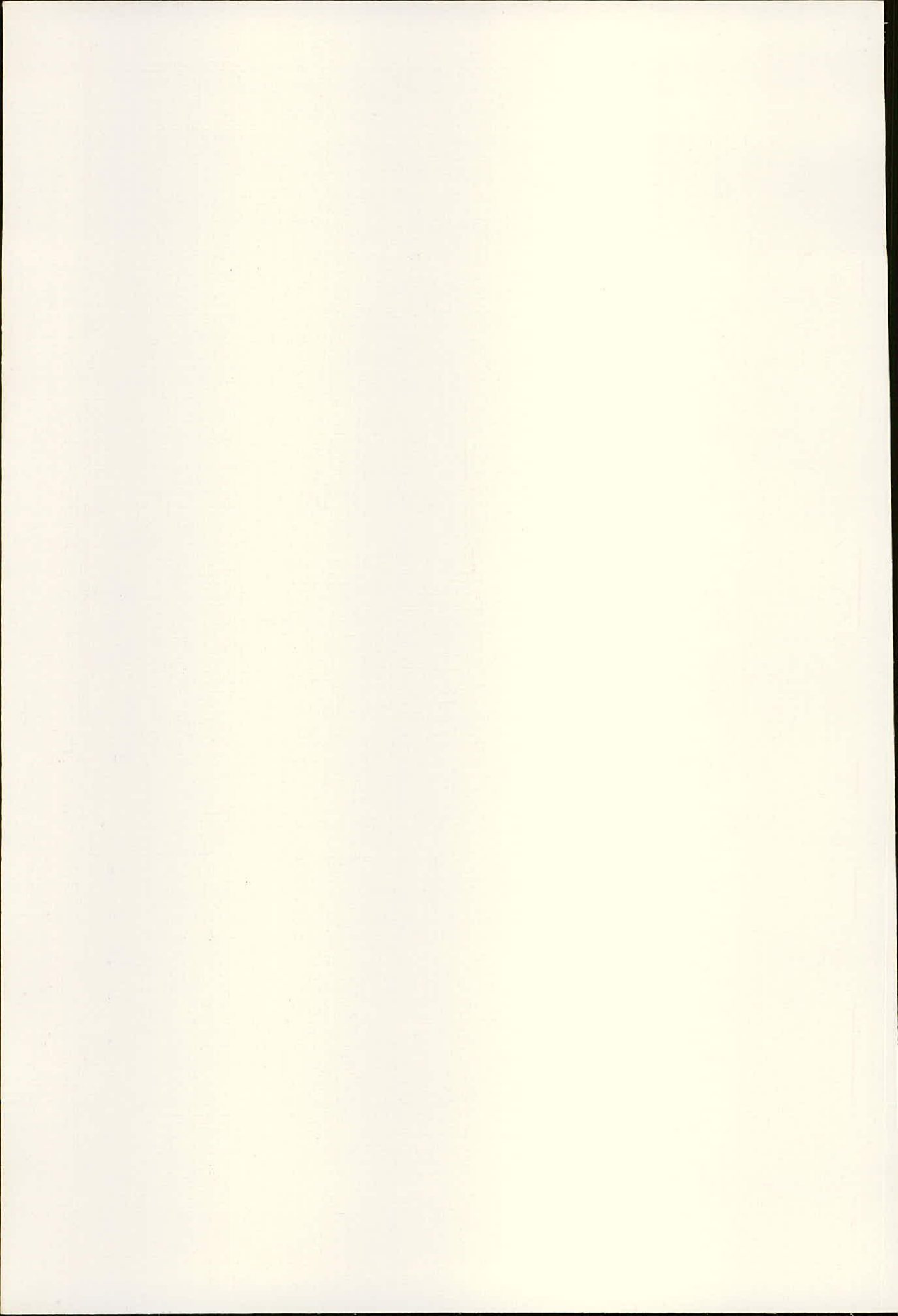
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Introduction and Aim of the Work



Introduction

Acetylation is a well documented example for pharmacogenetic variability in drug metabolism. Acetylation is mediated in mammals, including humans, by the hepatic enzyme group N-acetyltransferase. The rates of acetylation vary considerably between individuals, who may be categorized as fast and slow acetylators (*Weber and Hein 1985*). Acetylator phenotype had been, traditionally, used to predict toxicity from therapeutically used drugs as procainamide and isoniazide or to define dose requirements as for hydralazine (*Drayer and Reidenberg 1977*). However, correlation's between phenotype and different disease states have also been made. A number of studies suggest that idiopathic systemic lupus erythematosus (*Utrecht and Woosley 1981*) and tuberculosis (*Hanngren et al 1970*) are more common in slow acetylators while an increased proportion of fast acetylators has been found in diabetics (*McLaren et al 1977*).

The relation between the acetylator phenotype and the predisposition to different cancers had been suggested by many studies and was postulated to be linked to the activation / inactivation of environmental carcinogens. The most consistent association with acetylator status is that with urinary bladder cancer, particularly in populations with high risk due to occupational exposure to aniline dyes (*Wolf et al 1980, Cartwright et al 1982, Evans et al 1983*). It was postulated that slow acetylators are unable to acetylate aniline dyes and hence are being more susceptible to the carcinogenic effect of these compounds.



I. Malignant Lymphomas; Definition and History

While there are several chronic diseases more destructive to life than cancer, none is more feared.

Charles H. Mayo
(1865-1939), 1926

Malignant lymphomas, traditionally considered tumors of the lymphocytic system, are now considered as tumors of the immune system (*Banks 1995*). As cells of the immune system are widely distributed within all body organs, lymphomas can arise from, virtually, any site although certain organs; namely the lymph nodes, tonsils, spleen, and the marrow have the highest concentration of lymphatic tissue and are the principal sites of involvement (*Burke 1992*). While some forms of lymphoma tend to retain their cohesion to their organs of origin and progress as solid tumors, others tend to involve the marrow and the blood as leukemia. The distinction between lymphoma and lymphocytic leukemia is a function of organ involvement.

In 1832, Thomas Hodgkin published the first article on primary malignancies of the “absorbent glands” based on clinical and autopsy findings (*Hodgkin 1832*). Subsequently Virchow distinguished leukemia from lymphoma in 1846 (*Virchow 1846*) and coined the terms lymphoma (*Virchow 1858*) and lymphosarcoma (*Virchow 1863*). Billroth, in 1871, was the first to use the term malignant lymphoma (*Billroth 1871*). The earliest definition of clinical findings that characterize Hodgkin’s disease was made by Wilks in 1865 (*Wilks 1865*) which was reinforced by the description of the histopathological findings of Hodgkin’s disease by Sternberg in 1898

(*Sternberg 1898*) and Reed in 1902 (*Reed 1902*). The category of follicular lymphomas was initially recognized in 1916 by Ghon and Roman (*Ghon and Roman 1916*) and the category of large cell aggressive lymphomas was subsequently recognized by Roulet in 1930 (*Roulet 1930*). The first note on pediatric highly aggressive lymphomas, recognized 50 years later as lymphoblastic lymphoma, was made by Cooke in 1932 (*Cooke 1932*). By the middle of the twentieth century, clinically useful systems of classification were formulated. For Hodgkin's disease, the Jackson and Parker system (1947) followed by the Lukes, Butler, and Hicks in 1966 proposed six pathologic subcategories which were consolidated into the traditional four pathologic subgroups by Rye in 1971 as a modification of his original scheme of 1965 (*Linch et al 1999, Banks 1995*). Regarding the NHLs, and since the early 1940s, it was recognized that the follicular growth pattern as well as the predominance of small lymphocytes as the malignant cells is associated with a more favorable outcome (*Gall and Mallory 1942*) in contrast to NHLs where large cells with diffuse pattern of growth which are associated with an aggressive clinical course and poor outcome. Based upon the same principles, and with growing experience and precision, sequential classification systems were reported; those of *Gall and Mallory (1942)*, *Gall and Rappaport (1958)*, and *Rappaport (1966)*. During the 1970s, the Rappaport system revolutionized the choice of therapeutic modalities for NHLs as it had proved a high accuracy in predicting the response to therapy and hence was able to recommend more aggressive modalities based on histology (*Rosenberg 1979*).