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VINCALEUKOBLASTINE

THE results of treatment of cancer patients with any new drug are of great interest to the clinician and the experimentalist. This is particularly so if the agent used is not chemically related to those presently employed, or if there is evidence that it may exert a new type of action. Vincaleukoblastine (VLB), an alkaloid extracted from the plant *Vinca rosea*, was first isolated in the Collip Medical Research Laboratory at the University of Western Ontario and is presently under extensive studies for its possible use in the treatment of cancer. Preliminary observations by both American and Canadian workers were reviewed at the Canadian Cancer Research Conference[1] at Honey Harbour in June 1960, and indicated that further investigation of the effects of this agent should be undertaken.

The results of studies by two separate groups of workers in Toronto and Vancouver are reported in this number of the Journal and present an extensive series of cases now examined. These results are of considerable importance in that they suggest that certain types of malignant disease, particularly Hodgkin's disease, are especially responsive to treatment with VLB, and also since they indicate that the drug may be effective even though resistance has occurred to other forms of treatment. VLB exhibits a marked action on the hematopoietic tissues even after a single dose, and this may be a limiting factor to the dosage which may be administered. Characteristically, however, bone marrow recovery is rapid and a cumulative depression of the white blood cell count does not occur when repeated doses are correctly spaced. Favourable responses to treatment have varied in their duration but the optimum type of maintenance therapy has probably not yet been established.

The discovery of vincaleukoblastine by the Canadian research group has been cited to emphasize the role of chance, or serendipity, in experimental research. The plant, *Vinca rosea*, the common annual periwinkle, had enjoyed a popularity for many decades as the ingredient of a brew used as a family medicine for the treatment of diabetes mellitus. The initial interest in this plant, therefore, was to investigate orally administered extracts for their possible antidiabetic effects. During the course of these essentially negative investigations it was noticed that the injection of some fractions resulted in the rapid death of rats, apparently from overwhelming infection. Further experiments showed that there was an associated depression of the white cell count and marked destruction of some elements of the bone marrow. These effects were so marked, even after a single injection of the extract, that they were used initially as a biological assay method in attempts to chemically purify the active agent. With the observation that the white blood cells could be influenced, the problem then became at least of theoretical interest in the study of leukemia. The isolation of VLB as one active fraction of the plant allowed more extensive studies with this pure alkaloid. Its effect on bone marrow was pronounced, since as little as 0.3 mg./kg. in the rat caused a depression of the leukocyte count, in which granulocytes were virtually absent. Curiously enough, the action seemed to be quite specific, as platelets and megakaryocytes were unaffected. Similarly, despite the common deleterious action of many other agents on the gut, VLB showed little evidence of any such destructive action.

Tumours in experimental rats and mice were readily shown to be checked in their growth by doses of VLB which were well tolerated by the animals. In some cases apparent cures were observed. Although various mouse leukemias responded favourably, as might have been anticipated, a number of solid tumours were also affected. Circulating tumour cells seemed particularly sensitive to the action of VLB. It seemed well justified at that time to turn to cautious use of this alkaloid in advanced cases of cancer in humans. As supplies of such an alkaloid, present in only minute amounts in the plant, would rapidly have become a limiting factor, it was fortunate that Eli Lilly and Company also had been interested in the possible antidiabetic properties of the plant and had initially screened some extracts against mouse leukemia. With the publication of the method of isolation of VLB,[2] supplies were quickly made available for experimental clinic testing ("Velban" in U.S.A.; "Velbe" in Canada—Eli Lilly and Company).

Extensive series of clinical cases have now been treated with VLB in various centres, and such studies will no doubt continue to be the subject of further reports, in due course. The final assessment of the usefulness of VLB as a form of therapy for cancer must await further investigation. From the point of view of the experimentalist a number of points of interest have clearly emerged. Most

patients treated with VLB have previously 'escaped' from other forms of chemotherapy. Enough cases have responded to VLB to imply strongly that its mode of action must be by some new route. This offers the possibility of more effective combination or sequential types of therapy. In both experimental and clinical studies, mitotic metaphase arrest has been noted following VLB administration. Some evidence, however, indicates that this may not be its primary means of anti-tumour action. The action of VLB is curiously specific. Little evidence of a reduced platelet level has been encountered in patients who have received this drug, and gastrointestinal symptoms have not indicated the occurrence of destructive lesions of the mucosa. In the rat, regeneration of an organ such as the liver may proceed rapidly, although destruction of the bone marrow may take place simultaneously. The many types of malignant disease in humans which have shown regression, even if for only a brief period, suggest that this alkaloid may be affecting some process common to many forms of cancer. Why certain cancers are more susceptible or have longer remissions after regression remains an enigma, particularly since some solid tumours may be as responsive as the leukemias.

The mode of action and metabolism of VLB still await clarification, and will be speeded, particularly through the use of the isotopically labelled alkaloid. The discovery of some means of selectively protecting the bone marrow might allow the use of larger doses of VLB to exert a greater action on solid tumours. Further chemical studies are imperative, since the possibility exists that similar alkaloids may be isolated or that additional derivatives may be prepared which may have a qualitatively or quantitatively different action on malignant diseases not significantly affected by VLB.

R.L.N.

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OPPORTUNITIES FOR TRAINING IN RHEUMATOLOGY

NOT so many years ago the field of chronic rheumatic diseases held little or no attraction for the bright young graduate faced with a choice of careers in medical research or specialty practice. By and large, the attitude of the orthodox profession towards the unfortunate victims of this crippling and disabling group of diseases was all too often one of therapeutic nihilism, more than a few vestiges of which, it must be said, still persist. Gradually, however, since the First World War, the attitude of the profession towards this area of medicine has changed. Subtly and almost imperceptibly at first, this mounting interest in the rheumatic diseases gained momentum, stimulated by the contagious enthusiasm and intelligent guidance of such dedicated pioneers as van Breemen, Kahlmeter and Forestier in Europe; Fox, Sir Humphry Rolleston and Lord Horder in Britain; Pemberton, Wilson, Osgood, Haden, Cecil, Minot, Sturgis, Zinsser and Hench in the United States; and A. A. Fletcher and Wallace Graham in Canada. Eventually the study of the broad spectrum of rheumatic and connective tissue diseases expanded to the extent that it has become a full-fledged scientific discipline, in most centres as a subspecialty within the compass of internal medicine.

As was ever the case, when professional interest focuses on a particular segment of medicine, the inevitable result is that the disciples of this study band together to form a specialist society. In the mid 1930's the herd instinct of North America's rheumatologists expressed itself in the creation of those organizations now known as the American and Canadian Rheumatism Associations, both of which have since flourished and spread themselves like the green bay tree of the Psalmist. Worldwide concern with the medical and paramedical problems created by rheumatic and allied diseases is evidenced by the fact that similar specialist societies of national scope now exist in most major nations. The intense concentration of clinical and basic research in this field of medicine is reflected in the breadth and magnitude of subject matter which bulges the seams of the scientific programs of the International Congresses on Rheumatic Diseases, the tenth of which will be held in Rome about the time that this editorial appears in print.

The factors that have influenced the explosive expansion of interest in the rheumatic diseases since the Second World War are many and complex. Undoubtedly, one of these was the Nobel prize-winning discovery by Hench and Kendall, that certain steroids from the adrenal cortex could dramatically reverse the inflammatory manifestations of some of the rheumatic diseases.

Mounting concern over the magnitude of the problem posed by the ever increasing number of persons incapacitated by chronic illnesses and disabilities of all types, and the resulting ferment of activity in the broad field of rehabilitation of our disabled fellow citizens, likewise intensified professional and public interest in the plight of those who suffer from rheumatic disorders. In this relatively favourable atmosphere of general public concern the Canadian and American Rheumatism Associations began negotiations with appropriate government authorities and other interested groups which culminated in 1948 in the creation of the Canadian Arthritis and Rheumatism Society (C.A.R.S.) and its counterpart, the Arthritis and Rheumatism Foundation (A.R.F.), in the United States. The C.A.R.S. and A.R.F. are voluntary, non-profit, medico-lay organizations dedicated to the furtherance of research, professional and public