# Enkephalins and Endorphins

## Stress and the Immune System

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FOREWORD

Is this a time for a sleeping giant to rise? We have known since study of the lymphocyte and plasma cells really began in earnest in the early 1940's that the pituitary adrenal axis under intimate control of the hypothalamus could influence immunological functions profoundly. We have also known for at least 20 years in my recollection that female sex hormones can maximize certain immunity functions while male sex hormones tend to suppress many immunological reactions. The thyroid hormones accelerate antibody production while at the same time speeding up degradation of antibodies and immunoglobulins and thyroidectomy decreases the rate of antibody production. Further, much evidence has accumulated indicating that the brain, yes even the mind, can influence in significant ways susceptibility to infections, cancers and to development of a variety of autoimmune diseases. More than 20 years ago, my colleagues and I convinced ourselves, if no one else, that hypnosis can exert major influences on the effector limb of the classical atopic allergic reactions. We showed with Aaron Papermaster that the Prausnitz-Kustner reaction may be greatly inhibited, indeed largely controlled, by post-hypnotic suggestion. And it was not even necessary for us to publish our discovery because scientists in John Humphrey's laboratory at Mill Hill Research Center in London had beaten us to the punch. They described hypnotic control of both the PK reaction and delayed allergic reactions to tuberculin by hypnosis. Although he doesn't necessarily attribute the controls to neurological modulation, I have been convinced that the extraordinary rhythms Franz Halberg in Minnesota has elucidated for immunological functions that range from NK cell activity to the amount of antibody produced and even the tempo of allograft rejection reflect neuroendocrinological interactions with the immunological systems.

Halberg's Chronoimmunologic analyses have been underway for at least 20 years and would have begun earlier and progressed even more rapidly than they have had we immunologists been more responsive to his prodding and that of other chronobiologists associated with him.

Why then does the present moment strike me as so propitious a moment for a comprehensive new work considering the interaction of the major body networks?

For me, a new and truly golden age of psychoneuroimmunoendocrinology began when Wybran of Brussels first observed in 1979 that met-enkephalin

can talk to lymphocytes directly and its conversation with lymphocytes can be interrupted by naloxone. These rather crude beginnings have now been greatly refined and we know for sure that lymphocytes have receptors for met-enkephalin and have either surface or cytosolic receptors for a number of other hormones and neurohumoral mediators. We see in this volume and in numerous contemporary articles reaching our scientific journals that met-enkephalin, leu enkephalin and endorphins can reproducibly influence cell surface expression and functions of lymphocytes in vivo, antibody production, delayed allergic reactions and development and differentiation of lymphoid cells. We are even witnessing these days the first descriptions of responses of immunoparameters in healthy humans and patients with various kinds of immunodeficiencies including patients with AIDS and cancer. All this is happening right now and this science and this form of immunopharmacology will be rapidly developed in the years ahead.

But this is only one of many many exciting fields in psychoneuroimmunoendocrinology where incredible discoveries are turning up.

As a Visiting Professor at the University of Texas Medical Branch in Galveston last winter, I was introduced to a constellation of related studies by Blalock and his group of young colleagues. These studies established to my satisfaction that lymphocytes, like pituitary cells, can produce a molecule very like ACTH both immunologically and functionally and that like cells of the anterior pituitary, the lymphocytes have cytosolic receptors for cortisol. Through these, cortisol can suppress production of the ACTH-like molecule by these cells. As a classical cellular immunologist such a turn of events could never have entered my mind yet here it was, big as life, and it had been demonstrated by what seemed to me to be commanding and critical scientific methodology.

But these surprises are at least paralleled as surprises presented by Hall and Goldstein's (Washington) discovery that thymosin $\alpha_1$ now a fully defined molecule (thymic hormone?) exerts functional and electrical influences on certain hypothalamic nuclear cells that can, in turn, exert influences on lymphoid cell function through the thymus. If these descriptions sound fanciful it is because I believe they are. Yet they and much, much more are presented in detail in this volume of collected multi-authored papers that reflect a burgeoning scientific field. Even Robert Ader and Nicholas Cohen's exciting discovery that the immune response can be regulated by taste via prior conditioning in the conditioned -aversion response after simultaneous exposure to a cytotoxic immunosuppressive chemical may before long be explained in precise immunopharmcological terms. I now would bet it will.

This field is developing more rapidly than I thought could ever be the case and I am thankful to the immunopharmacologists like Plotnikoff, Wybran, Hadden, Szentivanyi and others who have urged me to pay close attention.

Robert A. Good, M.D., Ph.D.

CONTENTS

ENKEPHALINS-ENDORPHINS:
STRESS AND THE IMMUNE SYSTEM



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REGULATORY CIRCUITS OF THE IMMUNE, ENDOCRINE AND NERVOUS SYSTEM