Editorial

A Brief Historic Perspective On Research Related To The Human Immune System and Its Relationship To Endocrinology, Reproductive Endocrine Systems Metabolism, Cardiovascular and Neurological Conditions with the modulating effects of the female Menopause, Aerobic and Muscle Strengthening Exercise.

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Although the project I led and undertook was the first one of its kind, however, I feel that published related literature/ research done by others in the past should be discussed first.

Indeed it was not till the mid-1970s that interest was taken by physicians/ scientists in the effects of female hormones which were by then extensively used both for contraception and replacement therapy. The mechanistic approach to the immune system at this stage (although rapidly developing) was still in its infancy. Although a lot is known now many of the fundamental characteristics of both the endocrine (hormones) and the immune system are still not known and properly understood, the acquired immunodeficiency syndrome (AIDS) though not related to this study/ project is an example.

The inter-relationship of the immune and endocrine systems also referred to as immuno-endocrinology is also poorly understood. This review of related/ associated literature shall be presented with a historical perspective, hence in chronological order, and since I have the advantage of a retrospective approach to these).

The earliest reference which one can find in modern scientific literature8 was a study conducted by Albin et.al., in 1975 where they did the Dinitrochlorobenzene (DNCB TEST) test on 48 women who were on oral contraceptives. The DNCB TEST was a qualitative measure of

lymphocyte activity. They found a slight (statistically not significant) decrease in the cell-mediated immune response

Since pregnancy is associated with marked elevation of estrogen levels, besides the fetus itself may be considered as an allograft (like a transplanted organ) hence the role of the immune system gained attention. A study by Nobuyuki et al.9 found that the concentrations of the immunoglobulins IgG, IgA, and IgM decreased significantly in the second and third trimesters decrease in the level of IgM were found to be significant. The research group concluded that some immunosuppression occurs in pregnancy the mechanism of which is not known.

In 1978 Eskola et.al., published their study11 which saw the immediate effect of marathon running(2.5 hrs) and moderate running(35 min) on the total number of lymphocytes and effects of mitogenic stimulation (in vitro). (B cells & T cells) they noted a mild reduction in the mitogenic response

With the arrival of the 1980's, both prolific organ transplantation and the AIDS epidemic revived interest in the immune system. In organ transplantation, the controlled suppression of the immune system to prevent the rejection of the transplanted organ is an important part of the therapy. Among the most commonly used immuno-suppressants are corticosteroids. So several studies were conducted to see and understand their modulating effects on both humoral and cell-mediated immunity. Cupps and Fauci in their landmark paper12 give a detailed review of animal studies as well as their studies. They did report a reduction in the levels of IgG and IgA and a slight reduction in the levels of IgM after two to four weeks of corticosteroid therapy. Their observations on the cell-mediated immune response in vivo were rather confusing: ranging from no effect on the natural killer(NK) cells and ADCC (antibody-dependent cellular cytotoxicity) to a suppressive effect in some cases and surprisingly a stimulatory effect in a few of the cases. They summarized their conclusions: " Glucocorticoids have profound and complex effects on the human immune response.

An article written by J. Edwin Blalock13 received worldwide attention. In this essay, the writer presented ideas concerning the interaction of the immune, endocrine, and nervous system. Some of the ideas stemmed from the fact that cell biologists had recently discovered in 1983 that lymphocytes apart from secreting immunoglobulins, also secreted lymphokines, cytokines, and some hormones like the thyroid-stimulating hormone(TSH) and the adrenocorticotrophic hormone(ACTH).

It was well known at that time (and is still true) that when a human or animal is under stress ACTH is secreted in increased quantities to stimulate the adrenal glands to secrete more glucocorticoids to combat stress, hence Blalock hypothetically suggested a link between the immune, endocrine, and nervous system.

Experimentally Blalock demonstrated electrical changes in the hypothalamus of the brains of rats when their immune system underwent antigenic stimulation. This led him to theorize that the immune system had a sensory function also.

A group of physicians of the Department of Behavioral Medicine at Harvard University14 published a study where they investigated the effects of academic stress on the salivary secretion of IgA. The subjects were first-year students of the Boston University Dental School, they consisted of 48 males and 16 females, At all data collection points, it was observed that the mean salivary IgA levels were lower in all the 64 subjects as compared to the baseline values. A noteworthy point of this study was that a questionnaire regarding the difficulty of course work was given to each student at the time when saliva samples were collected. Students who reported more problems and difficulties in their studies had a proportionally greater reduction of their salivary IgA levels. Thus they verified their hypothesis that mental stress can temporarily down-regulate some facets of humoral immunity.

By the mid-1980s a lot of interest was generated on the effects of exercise on lymphocyte function at the cellular and molecular levels. Although these studies15,16,17 & 18 were concerned with only the cellular and molecular aspects with little emphasis on actual clinical and physiological effects, never the less they formed an important basis of our under-standing of some functions of the immune system and their modulators. I shall briefly discuss some studies.

The first study in this series was done by Brahmi et.al.15 at the University of Indiana. Their work “The effect of acute exercise on the natural killer cell activity in trained and untrained sedentary human subjects."

i. Natural killer cell activity immediately after exercise was significantly increased.

ii. Two hours after exercise the natural killer cell activity became lower than normal.

iii. Twenty hours after the exercise the natural killer cell activity became normal.

At about the same time of the publication of the above-quoted study Berk et.al.,16 presented their study at the annual meeting of the American College Of Sports Medicine: " The Suppressive Effect Of Stress From Acute Exhaustive Exercise On T Lymphocyte Helper/Suppressor Cell Ratio In Athletes And Non-Athletes treadmill (adopting the Balke protocol) and exercised to exhaustion. Blood samples were taken before and immediately after the exercise protocol. In both groups, they found a significant increase in the suppressor cells post-exercise, and a significant decrease in the helper cells post-exercise. Thus they concluded that acute brief heavy exercise would modify the immune response.

The previously quoted studies on the relationship of exercise and the immune system were all concerned with the immediate effects of acute exercise and that to aerobic exercise.

Drug or Alcohol Abuse.

A note-worthy point in all the studies done was that all of them only dwelt on the modulating effects of aerobic exercise, none of them dealt with the effects if any due to resistance training or muscle strengthening. One reason for this is due to the fact that at that time aerobic exercises were becoming very popular and our national obsession with resistance training (muscle strengthening) only started in the 1990s.

After the mid-1980's the attention of various investigators for some time focussed on the general metabolic changes produced by exercise and while investigating these metabolic changes they also measured changes in some substances which were recognized as immune mediators although their precise function was not clear

With the development of sensitive assay techniques, in A landmark study in this regard was done by T.A. Hewlett of the department of endocrinology at St. Bartholomews Hospital, London, England20. In this study Dr. Hewlet did not recruit a group or groups of research subjects, instead, he did a random measurement of various hormones after 20 minutes of vigorous exercise in a large category of humans, namely athletes, untrained persons, thin persons, obese persons, menstruating women, and diabetic persons.

He reported his findings hormone wise.

Growth Hormone: The levels of growth hormone after a bout of vigorous exercise increased considerably in untrained people (people leading a sedentary lifestyle) as compared to people who were trained athletes.

Cortisol and ACTH: Cortisol levels fell when the exerciser reached exhaustion.

Prolactin: No changes seen in women. But a small rise occurred in men.

Thyroid Hormones and TSH: There was a rise in the levels free of T3 and T4. No rise in the levels of TSH was noticed.

Gonadotropin's and Gonadal Steroids: In females, no changes in the levels of follicle-stimulating hormone (FSH), luteinizing hormone(LH) or estrogen levels were noticed. However, testosterone, DHEA sulfate and androstenedione levels rose.

In males both testosterone and LH levels rose.

Insulin: Plasma insulin levels fell in normal, lean, obese and diabetic individuals but insulin sensitivity increased due to a temporary increase in the number of insulin receptors.

Other Hormones: (a) Plasma Catecholamines (adrenaline and noradrenaline levels fell.

(b) Plasma levels of renin, aldosterone and vasopressin all increased.

This study pointed to a multitude of changes in the human Endocrine and Immune Systems due to exercise.

This historical perspective will continue (if permitted) in Subsequent issues of the journal.

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