INTRODUCTION AND GENERAL MECHANISMS OF HORMONAL ACTIONS

1.1. HISTORY AND SCOPE OF ENDOCRINE PHARMACOLOGY

Claude Bernard’s many brilliant contributions to medicine and science included the discovery of glycogen in 1857, but it was von Mering and Minkowski who performed the classic endocrine experiments involving the removal of the canine pancreas. During the intervening years, many unsuccessful attempts were made to isolate the active antidiabetic factor until Banting and Best infused an extract into a depancreatized dog on November 19, 1921 and brought about a reduction in blood sugar; it was this study that most likely gave way to the widespread acceptance of hormonal replacement therapy. About 4 years later, Abel successfully prepared crystalline insulin, which not only substantiated its importance in the etiology of diabetes mellitus, but for the first time introduced the concept that specific protein possessed inherent physiological activity. Of all the hormonal replacement therapies used in modern medicine, insulin treatment in the patient with diabetes mellitus remains of paramount importance. Recent successes in the synthesis of proteins with the same amino acid sequences as those found in human insulin have been achieved using bacterial systems. Such biochemical accomplishments could eventually lead to the obsolescence of using animal-derived insulins for the therapeutic management of diabetes mellitus in humans,

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thereby reducing the immunological differences between the pancreatic hormones obtained from different species.

Other classical endocrine experiments having less immediate clinical implication involved the concept of hormonal replacement. In 1929, Koch and associates used extracts of bull testes to demonstrate its stimulatory effects on comb growth in capons. The discovery of cortisone by Kendall in 1935 provided further impetus for the development of extraction and synthesis methodologies, culminating in the concept of hormonal therapies involving pathological states not characterized by hormone deficiencies. Nevertheless, it took more than a decade for sufficient amounts of cortisone to become available for the management of such diseases as rheumatoid arthritis. Hench, in 1948, is generally credited with the initial therapeutic use of cortisone in inflammatory states such as rheumatoid arthritis.

Although modern biochemistry continued to provide more highly purified hormone preparations, as well as the methodologies required for their chemical synthesis in some instances, the widespread use of hormones was not initiated until the 1950s or 1960s. This era witnessed the advent of synthetic hormones and the eventual development of the so-called "pill" or oral contraceptive. While interest in the control of fertility was referenced in the Ebers Papyrus in about 1550 BC, it was not until 1960 that the availability of an effective chemical suppressor of ovulation became a reality. On the basis of earlier observations, Pincus and co-workers established that steroids could effectively inhibit ovulation in rabbits. This inhibitory action was demonstrated using either natural progestogens or synthetic steroids such as norethynodrel (Enovid). By 1954, sufficient animal testing had been completed, and clinical trials were undertaken by Rock, Garcia, and Pincus in Puerto Rico. The U. S. Food and Drug Administration (FDA) approved the use of the first combination-type oral contraceptive, Enovid, a 10-mg preparation containing norethynodrel and mestranol, in November 1959. Many other oral contraceptive preparations have since been approved, and continuing modifications have been made in the doses and dosage formulations of these synthetic steroids. The history or the development of the pharmacology of oral contraceptives represents an excellent example of the ingenuity of the U.S. pharmaceuticals industry coupled with the scientific talents of its basic researcher and clinical investigator.

Many significant contributions in the field of endocrinology have not only resulted in a better understanding of hormonal disorders but have led to clinically useful therapies (Table 1-1).