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,
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 ther­
apies involving pathological states not characterized by hormone defi­
ciencies. 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 rheu­
mumatoid 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 ovu­
lation in rabbits. This inhibitory action was demonstrated using either
natural progestogens or synthetic steriods such as norethynodrel (En­
ovid). 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 develop­
ment of the pharmacology of oral contraceptives represents an excel­
lent 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).