CHEMICAL CONTRACEPTION

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To my wife, Margaret

The boldly prudent, the thriftily selfish and ambitious, the imaginative and poetic, the lovers of money and solid comfort, the worshippers of success, of art, and of love, will all oppose to the force of life, the device of sterility.

—George Bernard Shaw, *Man and Superman*

FOREWORD

The publication of *Physiology of Reproduction* by F. H. A. Marshall in 1910, and the serious challenge to American law in 1913 by Margaret Sanger, a daring social reformer who advocated birth control, marked in our time two new world outlooks. One was to put the physiology of reproduction in a respected position for scientific inquiry, and the other was to push forward the importance of birth control for the emancipation of women and for family planning. During the past 60 years, there has been much progress in the elucidation of the mechanisms of reproduction, especially in connection with the endocrine system, and during the past 20 years the control of population growth for our own survival has been very much stressed. Although various anecdotal contraceptive methods had been described since antiquity, an effective method had never been achieved that could be used with little or no association with the sexual act. Thus, the development of an oral contraceptive pill by the late Gregory Pincus and myself, with the endeavor of many people from 1951 to 1960, again marked a new advance in the application of academic knowledge to the welfare of the human race. The author of the present volume was trained at Cambridge University in academic research, and now is working for a well-known pharmaceutical house in America.

He has followed the trend of applying academic knowledge and has written a comprehensive survey of chemical means used for contraceptive purposes. This book has not only brought our knowledge concerning the various chemical means for control of fertility up-to-date, but has also pointed out many avenues for further research to improve contraceptive measures. It will be a very useful book not only for the research workers and the medical profession dealing with fertility regulation, but also for the government agencies and philanthropic institutions responsible for the support of research and development for the control of population growth.

M. C. Chang, Ph.D., Sc.D. (Cambridge)

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Preparation of the book was assisted by the enthusiastic efforts of Freya Graham in information research, Peter Consigny in art work and photography, and my loyal and energetic secretaries Kitty Krogh, Claire Frischmuth, and especially Marjene MacIntyre, who helped me prepare the final manuscript.

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1

INTRODUCTION

During eons of time—perhaps as long as 2 million years—the human race grew to the present total of 3 billion people. According to United Nations estimates, the passing of only 40 years will be required to add the next 3 billion people.

The excessive growth of population, which alarms demographers, is a comparatively recent phenomenon (fig. 1.1). Between the years 1650 and 1850, the world population doubled, reaching 1 billion. Only 80 years elapsed before the next doubling. At present levels of growth (70 to 75 million people per year), the population will number 4 billion by 1975.

This exponential growth rate is chiefly a product of better medical care and nutritional standards, resulting in fewer deaths than births (fig. 1.2). Life expectancy rates began increasing in the 1800s, coupled with a diminution of birth rates in countries undergoing industralization and improved agriculture. The crude birth and death rates then

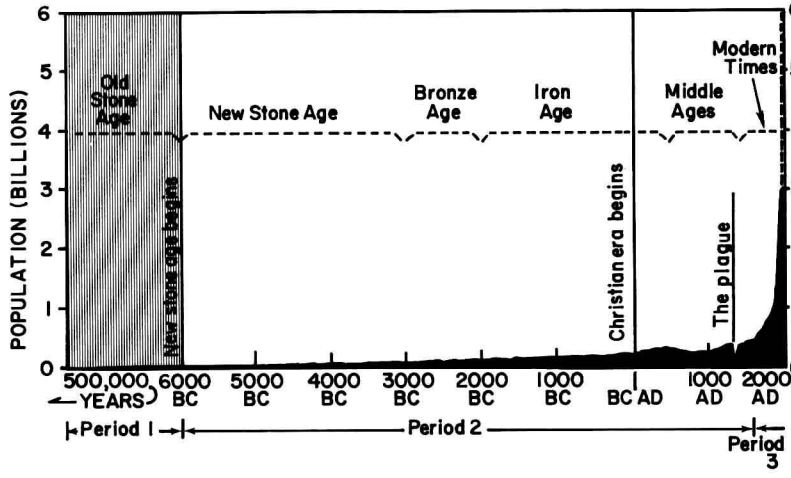

FIGURE 1.1
Population size through history. *Source:* Wellemeyer (1962).

remained almost parallel, but the numbers of births remained higher than deaths (fig. 1.3). In underdeveloped countries the life expectancy rate was not markedly increased until the late 1940s, when the use of DDT brought malaria under control and immunization suppressed many infectious diseases (e.g., smallpox). The sharp increase in life expectancy rates was not matched by a significant decrease in the birth rate, resulting in a very rapid rate of population growth. Unless the birth rates are lowered, the population growth rates will continue to rise until checked by an inevitable rise in the death rates.

The gross reproduction rates (the average number of daughters that would be born per woman who survived to the end of her reproductive period) range from 2.2 to 3.5 for most developing countries and from 1.0 to 1.8 for developed countries. Life expectancy rates range from 30 to 60 years for developing countries and from 67 to 72 years for developed countries. The difference between the gross reproductive rate and the life expectancy rate is a measure of population growth, which for most developed countries is between 0.5 and 1.7% per year and for most developing countries is between 2.0 and 3.5%. A 1.0% growth rate will produce a doubled population in 70 years, whereas a

3.0% growth rate will double the population every 23 years. Some countries have growth rates that are even higher (table 1.1).

The research required for new chemical contraceptives to curb such rapid growth rates has centered mainly in the developed countries. New contraceptives have mostly been designed for use by sophisticated populations. There has been little effort to seek antifertility agents for large-scale use in underdeveloped countries, with the exception of the intrauterine device (IUD).

The pharmaceutical industry is the most active body in developing new chemical contraceptives, since only it possesses sufficient financial resources together with the diversely skilled manpower necessary to carry development of a compound through the various stages of chemical synthesis and analysis, bioassay, toxicology, and clinical

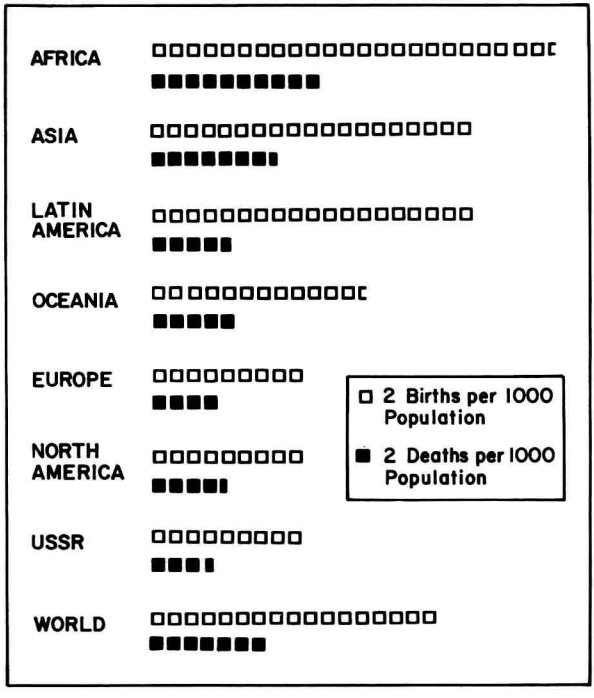

FIGURE 1.2
Present birth and death rates. *Source:* Population Reference Bureau (1970).

TABLE 1.1
COUNTRIES WITH GROWTH RATES HIGHER THAN 3.0%

Algeria	Jordan	Philippines
Colombia	Mexico	Southern Rhodesia
Costa Rica	Morocco	Sudan
Dominican Republic	Nicaragua	Surinam
Ecuador	Pakistan	Syria
El Salvador	Panama	Thailand
Honduras	Paraguay	Venezuela
Iraq		

Source: Population Reference Bureau (1971).

trials. However, many of the basic concepts leading to the discovery of original contraceptive methods are developed in university and government-sponsored laboratories.

Studies by pharmacists in the late nineteenth century, often in small shop laboratories, led to the introduction of the first widely used chemical contraceptives. An example was the development in England, by W. J. Rendell in the 1880s, of a quinine-containing suppository as a vaginal contraceptive. The company currently markets a vaginal chemical contraceptive of different formulation.

During the late 1940s and 1950s the method of intravaginal chemical contraception was further developed, with the introduction of many spermicidal drugs that vary greatly in their contraceptive efficacy and esthetic appeal, as described in chapter 2. A few of these contraceptives in novel formulation, such as creams, gels, or aerosol foams, are used by large numbers of women.

The introduction in the 1960s of the extremely effective, ovulation-inhibiting hormonal contraceptives revolutionized the available methodology by separating the contraceptive method from the timing of intercourse. A detailed description of these "first generation" hormonal contraceptives appears in chapter 3. These contraceptive drugs have been subjected to extraordinarily detailed biological and clinical studies, because they are the first compounds given daily for prolonged periods to healthy people. The oral hormonal contraceptives are now used by approximately 10 million women in the United States and perhaps 30 million women worldwide.

In the late 1960s, attempts were made to improve the safety and efficacy of hormonal contraceptives. The downward titration of the

steroid contraceptive dose led to the discovery of the minipill, which prevents pregnancy at steroid doses below those inhibiting ovulation. The minipill exhibits lower side effects and only slightly lower contraceptive protection than that shown by ovulation-inhibiting doses of steroid. After more than 10 years of development, the minipill will play a role in contraceptive usage during the later 1970s as the "second generation" of oral contraceptives.

Further development of hormonal contraceptive steroids occurred during the late 1960s and early 1970s in the research laboratories of the major pharmaceutical companies. A search was made for improved systems of drug delivery to the target organs, in hope of minimizing the total dose required for protection against pregnancy. New steroidal formulations were developed as injectable solutions, subcutaneous pellet implants, and intravaginal tablets, and for inclusion in suppositories and intravaginal and intrauterine Silastic devices. Some success has been achieved in the development of these new

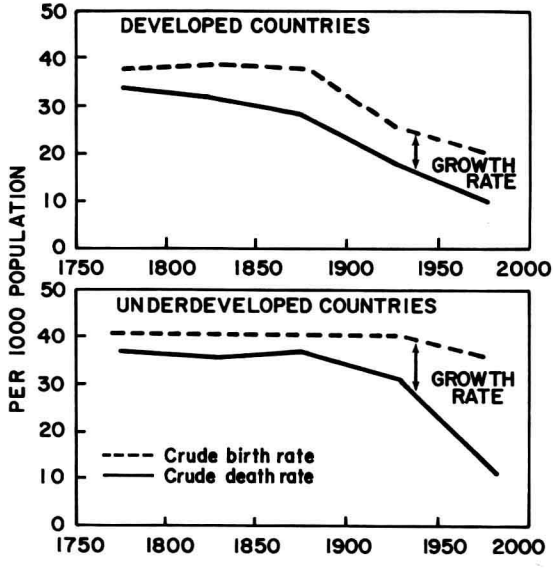

FIGURE 1.3
Estimated birth and death rates, 1770–1970. *Source:* United Nations (1971).

methods but, as recorded in chapter 4, a completely satisfactory depot contraceptive method for large-scale use remains unavailable.

During recent years, chemical contraceptive research has concentrated in the search for menses inducers, abortifacients, postcoital or postovulatory antifertility substances, and an active male contraceptive, with minimal side effects. The extensive studies described in chapters 5, 6, and 7 illustrate the immense amount of research conducted in these fields. Some important chemical contraceptive leads have been established. However, because of the demands of governmental drug regulatory agencies for extensive data on drug safety and efficacy, it is extremely doubtful that any of the new generation of contraceptives will be in wide public use until the next decade.

2

EARLY CHEMICAL REGULATION OF FERTILITY

THE SPERMICIDES

Thousands of years ago the Egyptians used intravaginal chemical contraceptives to prevent pregnancy. One of the methods used was acacia spikes ground finely with dates and honey, rubbed on a wad of fibers, and inserted deep into the vagina (Thorwald, 1962). Acacia spikes were later found to contain a gum that forms lactic acid, a substance contained in many of the spermicides used at present.

Early vaginal spermicides were developed of necessity in the home from common household materials, such as vinegar in a concentration of 2 tablespoons to a cup of water or lemon juice at 1 tablespoonful to the pint (Gamble, 1953). Ordinary table salt has been used in a 20% solution. In recent times, the contents of a well-shaken cola bottle have often served as both vaginal douche and spermicide. These primitive methods, although better than nothing, were ineffective and often bore the added disadvantage of producing vaginal irritation.