

Preface

A happy chance led to my interest in the subject of this book, an invitation out of the blue from the editors of the *New England Journal of Medicine* to write a review of the causes of congenital malformations in human beings as they were then known. Years earlier Josef Warkany, a pioneer in the field of teratology, and I had reviewed the same subject in the same journal (Warkany and Kalter 1961), and feeling it would lead to a stronger statement I asked him to join me in its writing.

The work that emerged rested on a critical reading and analysis of the biomedical literature of the previous several decades that dealt with congenital malformations and their causes, known and supposed (Kalter and Warkany 1983). These primary sources—reports of individual cases, hospital series, population surveys, vital statistics, and the like—contained many suspicions and allegations as well as some clear evidence about the origins of these abnormalities. Our task was to consider this body of evidence and come to an assessment of them for the purpose of estimating the likelihood of preventing such conditions.

The causes had earlier been broadly categorized into genic, chromosomal, environmental, and complex or unknown. About the first two generally there was little theoretical that was not settled, but about the others there was little that was certain. Thus the environmental origins of congenital malformations would get most of our attention, especially as that was where the controversies lay. A considerable number of such agents had been found to be teratogenic in laboratory animals. But no more than a handful had been unquestionably identified as having caused congenital malformations in human beings. These were ionizing radiation, already identified by the 1920s; the rubella virus, revealed in 1941; later some other infectious agents; and afterward several therapeutic substances, environmental contaminants, and a miscellany of others—cytotoxic, anticoagulant, and anticonvulsant drugs, thalidomide, organic mercury, and so forth.

In addition some noninfectious maternal illnesses were thought to cause or be associated with fetal maldevelopment; most of them seldom occurring however—except for one, insulin dependent diabetes mellitus. Years of study had made ever more firmly entrenched the belief that children of women with diabetes had an increased frequency of serious congenital malformations. This disease was intriguing. First, it was common in populations generally, and hence diabetic pregnancy was

common as well. Next it appeared to be a constant feature of the human constitution, not waning and waxing as did infectious diseases. And last it seemed to me that the long-held belief in its teratogenicity had not been closely scrutinized and needed further looking into.

Writings on the subject of pregnancy in diabetic women, beginning with those from the decades before the discovery of insulin in 1921, were voluminous and needed becoming acquainted with. Reading these pages, sometimes opaque and fragmentary, led to the report presented here.

A History of Diabetes in Pregnancy

The impact of maternal diabetes on offspring prenatal
development and survival

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