

imals in such high incidences that the endocrine stimulation may play a considerable, rather than an incidental, role."<sup>93</sup> A paper published a few years later argued, moreover, that cancerous and precancerous changes were induced by "prolonged and *not necessarily excessive* administration of oestrogens" (emphasis in original).<sup>94</sup> A 1944 article in the *New England Journal of Medicine* had warned physicians "against indiscriminate and excessive dosage with diethylstilbestrol," concluding: "Since our knowledge of the possible carcinogenic role of the estrogens is still very incomplete, it is a wise policy to avoid unnecessarily large doses and to avoid such treatment altogether or hold it to a minimum for persons who [are particularly susceptible]."<sup>95</sup> (By 1947 Karnaky was giving some women as much as 24,050 mg of DES.)<sup>96</sup> And in 1947, the *Dispensatory of the United States of America*, an encyclopedia of medical and pharmacological information, issued a prophetic warning:

To date no national catastrophe [sic] has been recognized, but it is perhaps too early for any deleterious effect on the incidence of carcinoma of the female generative tract or breast to appear.<sup>97</sup>

Also not mentioned in the manufacturers' supplemental applications was the possibility that DES could be hazardous not only to the women taking it but to the exposed fetus. By 1947 it was well known, at least among endocrinologists, that hormones and other substances could cross the placenta and affect the developing fetus.<sup>98</sup> Karnaky himself, in one of the studies cited by manufacturers, had observed that all of the DES-exposed babies carried to term "exhibited a darkening of the areolae around their nipples, labia, and linea alba, similar in intensity to that of their mothers, indicating that this effect of diethylstilbestrol also is shared by the fetus" (emphasis added).<sup>99</sup> Research on animals had shown that fetuses exposed in utero to exogenous hormones and other substances frequently developed various physical abnormalities. Beginning in the late 1930s, a number of studies on "experimental intersexuality" described what happened to animal offspring when pregnant females were treated with estrogens, including DES. The findings revealed, among other things, that female rat offspring developed enlarged uteri and structural changes in the vagina and ovaries, and that male rat offspring had small and inadequately developed penises and other sexual deformities.<sup>100</sup> Even the possibility of intrauterine exposure leading to carcinogenic changes