Letters

Emigration: A Safety Valve

Keeleric's letter (28 Aug.) makes a rather one-sided point about foreign immigration into the United States. His thesis seems to be that the citizens of this country owe the world (or certain parts of it) a living for the "4 million skilled or educated adults ready made" whom we "import" every decade. As a former denizen of the underdeveloped country from which Keeleric writes, I am only too well aware of the other side of the argument—that the United States has provided and continues to provide an opportunity for millions of people born outside its shores to develop their potential as intelligent and constructive human beings, an opportunity which their own countries have too often denied them. Add to this fact that, without the safety valve of emigration, some countries (including Keeleric's) which fail to provide acceptable standards of living for many of their citizens who do remain behind, would long ago have faced economic catastrophe, and one is left wondering who indeed is the actual "beneficiary of a huge foreign aid program."

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Demulen: Hastily Approved Drug

In Southwick's otherwise reliable and perceptive news article "FDA: Efficiency drive stumbles over the issue of drug efficacy" (18 Sept., p. 1188), he refers to a 40-volume British study of the oral contraceptive Demulen and to the American study of this drug. His statement confuses the two studies and their roles in G. D. Searle & Company's new drug application (NDA).

The entire NDA submission for Demulen consisted of 40 volumes, including the American study. The latter, conducted under an investigational use exemption, involved only 82 patients treated for four cycles and provided no useful data in support of the company's NDA. The British study alone was relevant to the new drug application.

While the British study included a total of 987 women, only 112 were treated with Demulen for 24 or more cycles—far short of the minimum of 200 to 300 patients required by FDA's established guidelines for demonstrating the efficacy of an oral contraceptive. Moreover, the British data were further inadequate in that the application did not provide the results of any of the numerous laboratory studies that are required to demonstrate a drug's safety. According to FDA's own review of the application, there was not a single blood test in any of the patients, and "some" of the women had Pap smears. In accepting the British data, FDA also violated its regulation requiring most of the clinical studies for an NDA to be conducted by qualified U.S. investigators.

Because of these deficiencies, the medical specialists responsible for reviewing the Demulen application were unable to approve it, and the NDA was sent to the director of the Bureau of Drugs for disposition.

In the final analysis, the FDA case for approving Demulen rests on these assumptions in place of the evidence required by law:

1) because pharmacologic studies have shown the estrogenic potency of ethinyl estradiol to be 1½ to 2 times that of mestranol (of which it is the principal metabolite) on a quantitative basis, one would expect a combination of 1 milligram ethynodial diacetate and 50 micrograms ethinyl estradiol (Demulen) to be as safe and effective as the same progestogen combined with 100 micrograms mestronal (Searle's Ovulen, already marketed). Also, one would expect to extrapolate all data from Ovulen to Demulen; and

2) because no pregnancies occurred in the British study, the efficacy of Demulen was demonstrated.

For the crowning irony, as a condition of approving Demulen, FDA will require Searle to conduct all of the phase III clinical studies that were originally called for by FDA's regulations and guidelines. These studies, involving at least 300 patients taking Demulen for 24 cycles, will take a minimum of 2 years during which the drug will be sold without any special restriction.

The hearings left unanswered the question of whether Demulen actually provides the physician and patient with a lower dosage of estrogen than Ovulen. The FDA witnesses were unable to give any estimate whatever of the frequency with which a woman would obtain less estrogen from Demulen than from Ovulen.

In this connection, the subcommittee questioned Searle's advertising for Demulen which suggests this drug contains one-half the estrogen content of other oral contraceptives and offers greater safety with equal effectiveness. Following the hearing FDA agreed that the Demulen ad is misleading and requested the manufacturer to discontinue it. It is noteworthy, also, that FDA mobilized its relatively scarce professional resources to give very high priority attention (involving overtime work) to the 7-day approval of a product which the agency's medical director characterized as a "me too" drug.

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A Base for Predicting Success

In his letter on college grades as predictors (3 July), it appears that Lindgren has confused his academic mythology. The "myth" that college grades are unrelated to performance or success later in life is in fact supported by considerable evidence. Hoyt's review (*1*) of 46 studies in this area found that "college grades bear little or no relationship to any measures of adult accomplishment." This absence of any significant relationship was observed across a variety of areas including business, teaching, medicine, scientific research, and nonvocational accomplishment.

Lindgren's "overwhelming evidence to the contrary" consisted of two studies. One study (*2*) found a slight positive relationship between self-reported college grades and earnings. Since the data in this study are pre-