

a one-month period of treatment by diet alone or who, during this one-month period of observation, were judged unable or unwilling to follow the study protocol; and (4) those who had any serious condition that in the judgment of the clinic physician, implied a life expectancy of less than five years.

As a result, the UGDP subjects may be thought of as a group of patients with adult-onset, nonketotic diabetes. There was a preponderance of women, who made up 71% of the total. Diabetes ranged in severity from asymptomatic, with no glycosuria, to symptomatic, with permanent glycosuria and marked hyperglycemia. A description of the patients is given by the UGDP (4, pp. 777-783) in the form of several tables that present distributions of base-line characteristics of those in the study.

In the UGDP, many of the criteria for excluding subjects were well defined. There were also situations, however, in which the clinic physician had to use his judgment—for example, in screening to obtain patients with a minimum life expectancy of five years. In view of this and of the fact that patients were drawn from various sources, it would be expected that clinics might differ systematically in the characteristics of the subjects selected.

3.1.2 Randomization and allocation of treatments

The UGDP study was arranged as a balanced design, stratified by blocks of 16 and 14 successive patients within clinics but without other restrictions on the pattern of assignment of treatment to subjects. Initially, during 1961 in each of seven clinics, the four treatments—variable-dose insulin (IVAR), standard-dose insulin (ISIB), tolbutamide, and placebo—were allocated randomly to patients in blocks of 16—four subjects in each of the four treatments in random order. In 1962-1963, phenformin was added to the treatments at five new clinics as well as at one of the original seven and, in order to achieve overall parity in the total number of patients assigned to each treatment, the block size was fixed at 14, with each block containing six subjects receiving phenformin, and two receiving each of the four other treatments.

For purposes of administrative efficiency, individual patients receiving tolbutamide or placebo were not assigned uniquely identified medication, but were supplied as follows: For the tolbutamide assignments, numbers 1 to 24 were split at random into two groups of 12, one group on numbers being assigned to placebo and the remainder to bottles that would be used for tolbutamide. Each of the first 24 subjects receiving placebo or tolbutamide in a given clinic was allotted a separate bottle number, the sequence then being repeated. Bottles 25 through 48 were used for patients assigned to tolbutamide in the clinics that also used phenformin.

As a consequence of this arrangement for the distribution of medication, sometimes two and as most three subjects in a given clinic were supplied with identical bottle numbers. The administrative advantage of this scheme is that each clinic could be given an initial supply of 48 uniquely labeled medications and could order additional supplies, as need arose, without burdening the central pharmacy with responsibility for more than 800 separately labeled medications.

The orally given medications in the tolbutamide study were in tablet form. The introduction of phenformin in the second part of the study required a change in the method of administration, since phenformin is supplied as granule-filled capsules. In this part of the study all control medication for new patients was given as capsules. Tolbutamide was still supplied as tablets but, unknown to the participating clinics, placebo in the form of tablets was not given in the phenformin clinics. New bottle numbers (49 to 72) were used for the capsules, but the same method of resupply was employed.

In executing this plan, lists of ordered treatment assignments were prepared in advance for each clinic by the Coordinating Center. Random permutations of 16 from the tables given by Cochran and Cox (15) were used for the treatment allocations in the first six clinics, and the Rand tables (16) were employed for those clinics in which phenformin was administered. The assignments were entered in a log book, and space was left on each list for entry of the name and identifying number of the patient and the date of assignment. To facilitate initiation of treatment, assignment requests could be made by the clinic to the Coordinating Center and filled by telephone, in which case a limited number of individuals had authority to record the name of the patient on the