The paper investigated whether the variability in the metabolism of isoniazid represented a genetic polymorphism. Using data from a study of 53 families, it was found that isoniazid metabolism is inherited as a Mendelian character. (The SCP* indicates that this paper has been cited in over 345 publications.)

A simple test that could be performed in a standardised manner on a large number of people (mostly healthy) was the next requirement. A single plasma isoniazid concentration determined six hours after an oral dose of 10 mg per kg body weight was chosen for this purpose. Unrelated healthy individuals were studied to see whether there were (as had been suggested by previous work) distinctly different types of individuals indicating different phenotypes. This survey revealed that the population resolved itself naturally into two types—slow and rapid metabolizers. Models of the genetic analyses likely to be required were available from studies of blood groups and phenylthiocarbamide.

An extensive family study proved that isoniazid metabolism was inherited as a Mendelian character. This finding was at the time innovative. In due course—after establishing a "liver bank" (stored samples of human liver)—it was shown that the enzymic basis lay in the activity of N-acetyl transferase. Other drugs have since been shown to be subject to the same polymorphic acetylation. Associations have been demonstrated between clinically significant events (especially adverse reactions) and particular phenotypes. More recently the polymorphism has been shown to have relevance to spontaneous disorders. Cancer of the bladder is a disorder more common in slow acetylators because they are less able to detoxify the causative aromatic amines. This finding is of especial significance to the discipline of occupational medicine. Associations of acetylator phenotypes with other disorders have been discovered as statistical phenomena with as yet no biochemical explanation.

The cited study was one of a small number of publications that formed the basis of an interdisciplinary branch of medicine termed "pharmacogenetics." A substantial number of other enzymic polymorphisms (especially those involving P450) influencing drug metabolism, as well as polymorphisms of pharmacologic responses, have now been described that are relevant to the clinical use of a large number of drugs.

It is probable that this 1960 paper has been cited so often because it presented a clear-cut conclusion of interest to workers in different fields of endeavor, for example, human genetics, pharmacology, clinical medicine, toxicology, and epidemiology.

Involvement in this project led to an academic career that brought me a number of honors including the first Sir Henry Dale Lecture, Membership of the Johns Hopkins Society of Scholars, and chairmanship of the Department of Medicine at the University of Liverpool, England.