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FORTY YEARS OF MOLECULAR MODIFICATION

How the Sulfa Drugs Emerged and Evolved into Diuretics, Carbonic Anhydrase Inhibitors and Antidiabetics

George H. Schneller, Ph. D.
Wyeth Labs., Box 8299
Philadelphia, Pennsylvania 19101

The emergence of sulfonamide compounds as antibacterial agents during a period extending from the 1930's through the 50's--and their further evolution into other areas of therapy during the next two decades--was one of the most remarkable therapeutic events of all time. Tremendous gains in human welfare accrued from the investigation of thousands of compounds during that period.

It is necessary to begin by briefly reviewing the early history (Figure 1). The first sulfonamide found effective in combating a systemic infection was Prontosil, in 1932. This compound--colored red by reason of its azo group--emerged from a great

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Adapted from a paper read before the Economics & Administrative Science Section of the Academy of Pharmaceutical Sciences, American Pharmaceutical Association at Orlando, Florida, November 16, 1976.

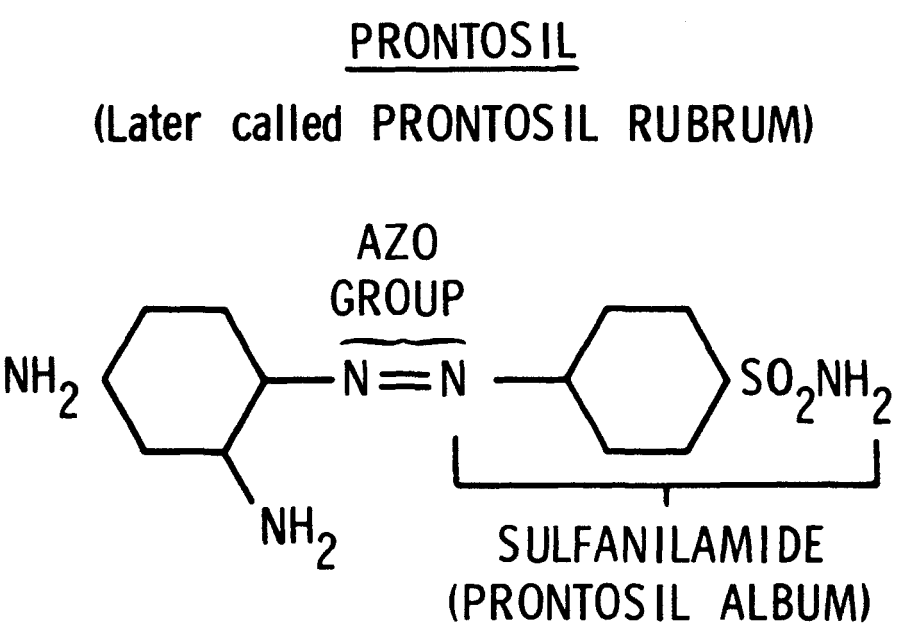


Fig. 1

deal of research by many leading chemists of the time in the field of azo dyes, a number of which were known to have antibacterial activity in vitro, but not in vivo. After it had been placed on the market, it was discovered that its activity was not dependent on the dye structure, but was wholly due to its metabolic product, sulfanilamide. (Following this discovery, the name of Prontosil was changed to Prontosil Rubrum to distinguish it from sulfanilamide, which was called Prontosil Album in some European countries and which, naturally, quickly replaced its progenitor in therapeutic use.)

Sulfanilamide was the first sulfonamide to gain widespread use in the United States. A dramatic demonstration of its value involved a son of President Franklin D. Roosevelt who developed septicemia from a broken blister suffered while playing tennis, and recovered after treatment with the drug. Not many years before, the son of another President--Calvin Coolidge--had undergone the identical experience and died from the infection.

The clinical success of sulfanilamide led to an intense search for analogs active against other pathogenic bacteria and/or less toxic. Of many hundreds of compounds studied, the first exciting one was sulfapyridine, (Figure 2) synthesized in 1938 at the British pharmaceutical firm of May & Baker. It had a remarkable curative effect in pneumococcal pneumonia. However, it was poorly tolerated, with an incidence of 25 to 40% of nausea and vomiting. Because of this handicap, and the need for compounds with still broader antibacterial spectra, the intensive search continued, and led to the discovery of sulfathiazole, which had the activity of both of its antecedents, and in addition was active against staphylococci. With this advantage, and also because it was better tolerated than sulfapyridine, it quickly supplanted the latter. But sulfathiazole itself caused nausea and vomiting in up to 10% of cases, and also caused skin rash and drug-induced fever quite frequently. Accordingly,

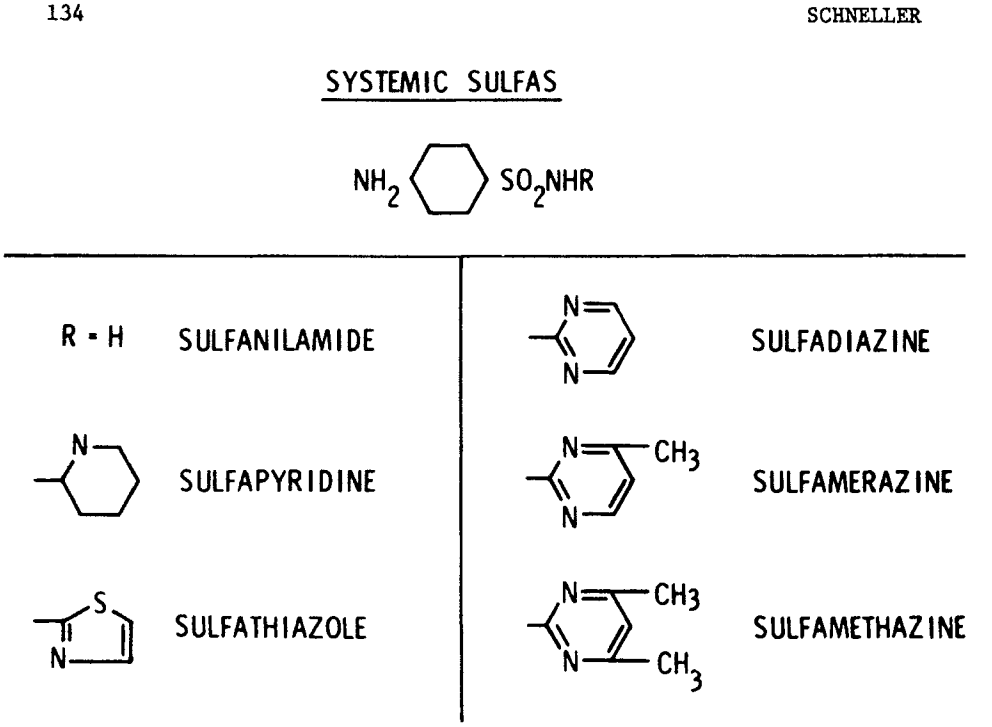


Fig. 2

when the sulfapyrimidines appeared--sulfadiazine and its monomethyl derivative, sulfamerazine, with a much lower incidence of these and other side effects, they replaced sulfathiazole in clinical use. However, because of the relatively low solubility of both drugs and of their principal metabolic products (the N^4 acetyl derivatives) they did not solve the problem of serious renal damage occasionally resulting from the deposition of crystals in the collecting tubules or elsewhere in the kidney. But it was found that employing mixtures of

these sulfonamides in the same total dosage reduced this risk, because of the additive solubilities of the individual components, without a sacrifice of effectiveness. When sulfamethazine became available (it had already become the leading sulfapyrimidine in Great Britain as a single drug) the combination of three sulfapyrimidines virtually eliminated the possibility of significant crystalluria.

Now, let us take a bird's-eye view of thirty-five years of sulfonamide therapy as reflected by the listings in the official compendia (Figure 3). Because of space limitations on a single slide, I have divided the drugs into therapeutic groups. The years indicated are those when the drugs appeared in the complete revised volume: some of them may have been added a couple of years earlier by interim revision. We can see that sulfanilamide remained in the U.S.P. for three revisions before deletion, was picked up by the N.F. for two revisions, and then disappeared. Sulfapyridine was dropped by the U.S.P. as soon as the advantages of sulfathiazole had become manifest, but later returned when its specific utility in dermatitis herpetiformis had become established. Sulfathiazole in turn dropped out of the picture as sulfadiazine and sulfamerazine proved to be superior. Sulfamethazine was admitted to the U.S.P. as the most rational third ingredient in triple sulfas, as we shall see

SYSTEMIC SULFAS

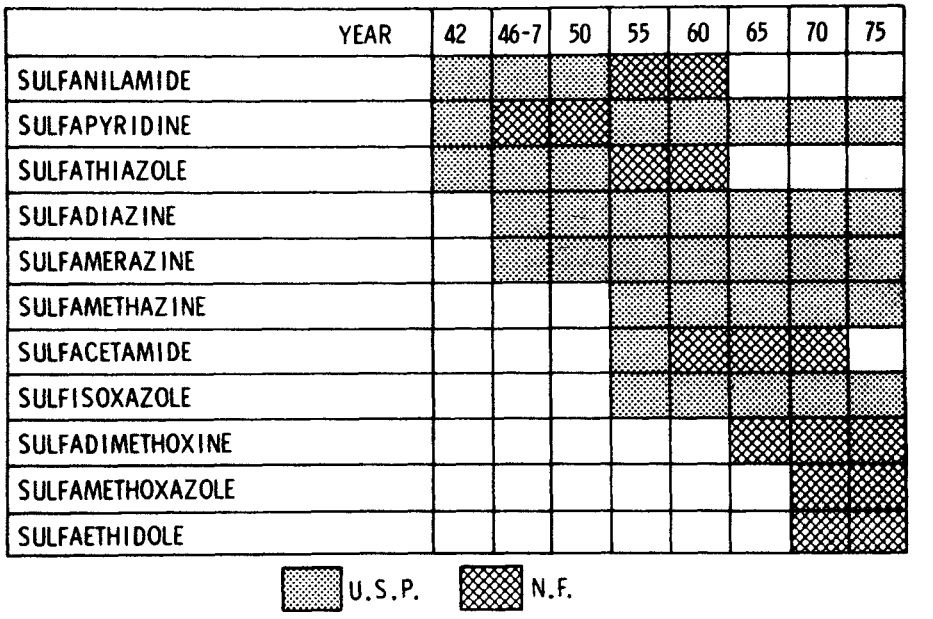


Fig. 3

later. Sulfacetamide (the N'acetyl derivative of sulfanilamide) and sulfisoxazole are included in this slide because they were originally used for some systemic infections. However, they are rapidly excreted, providing relatively low blood levels but high concentrations in the urine, in which they are freely soluble. Their clinical application proved to be primarily in urinary tract infections. Finally, we see three additional compounds admitted to the National Formulary in recent revisions.

In the field of intestinal sulfonamides (Figure 4) sulfaguanidine was very widely used by the armed forces during World War II and prevented any major epidemic of bacillary dystenery In civilian use it was superseded by the N^4 succinyl and -phthalyl derivatives of sulfathiazole which liberate low concentrations of sulfathiazole in the intestinal tract. Phthalylsulfacetamide had an analogous action, but never gained wide acceptance. Finally, sulfasalazine has become official after many years of use in the treatment of ulcerative colitis. Its mechanism of action is still not clearly understood. As might

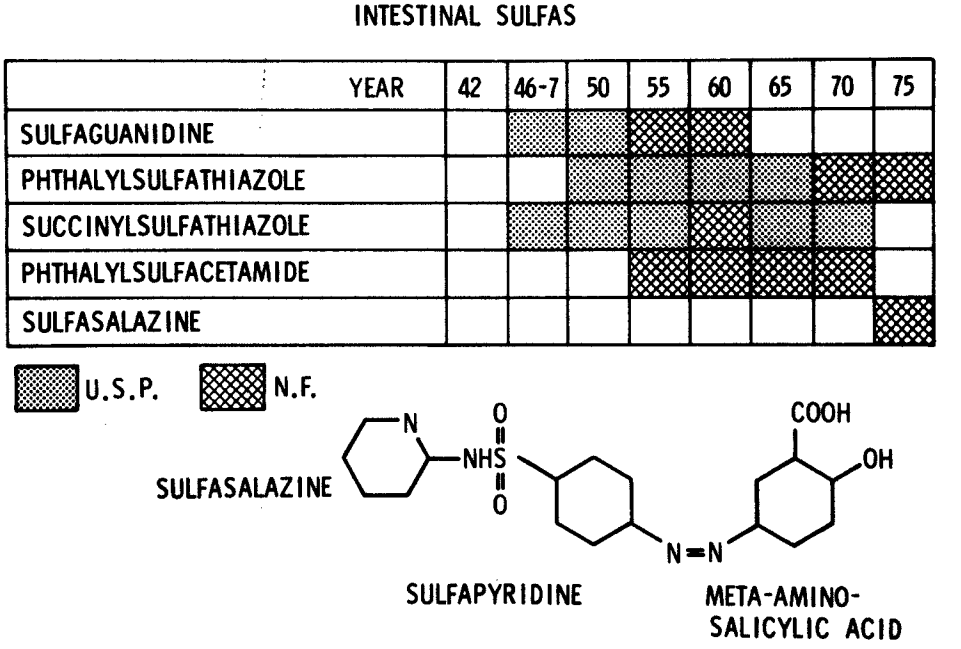


Fig. 4

be expected from its unusual structure, it is known to liberate sulfapyridine and meta-aminosalicyclic acid in the body. The drugs used in urinary tract infections are shown in Figure 5 and the soluble salts which are used in the treatment of infections of the eye in Figure 6. To complete the list of sulfa drugs in current use, Figure 7 shows certain non-official

URINARY SULFAS

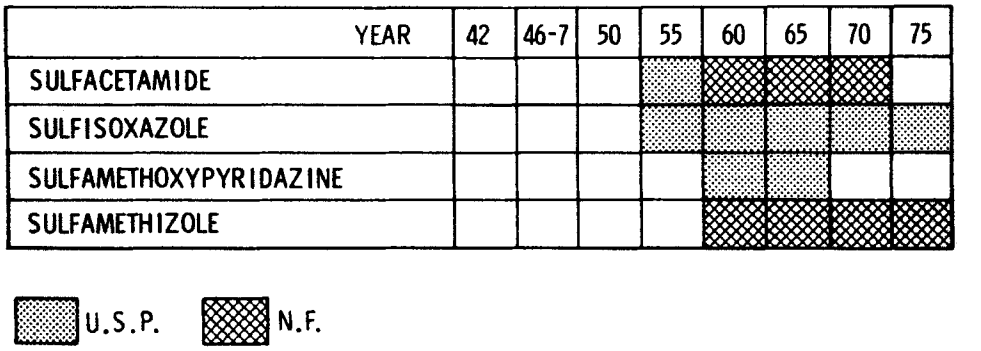


Fig. 5

OCULAR SULFAS

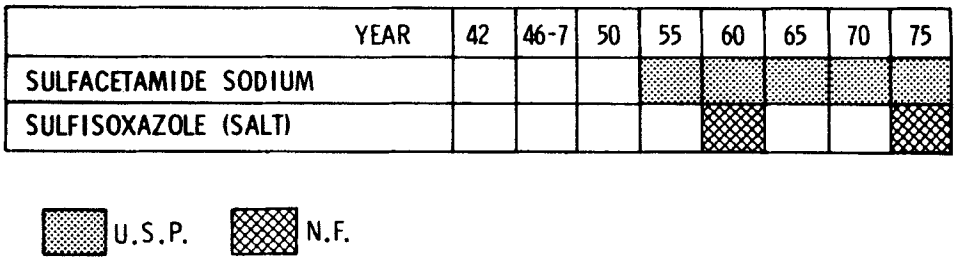


Fig. 6

ADDITIONAL SULFAS
(Listed in PDR 1976)

SULFABENZAMIDE	(IN VAGINAL PREP'NS)
SULFACHLORPYRIDAZINE	URINARY
SULFACYTINE	URINARY
SULFAMETER	URINARY
SULFAMETHIZOLE and PHENAZOPYRIDINE	URINARY
SULFAMETHOXAZOLE and PHENAZOPYRIDINE	URINARY
SULFAMETHOXAZOLE and TRIMETHOPRIM	URINARY

Fig. 7

compounds and combinations listed in the 1976 Physicians Desk Reference.

The official combinations in Figure 8 illustrate two types of advantages that can be gained from the use of combinations of active drugs. Trip sulfapyrimidines is a classic example of the use of several similar active drugs, each in reduced dosage, to achieve the same therapeutic effect with reduced toxicity. The toxic phenomenon targeted is primarily the physical one of crystal formation. Other toxic side-effects are probably also

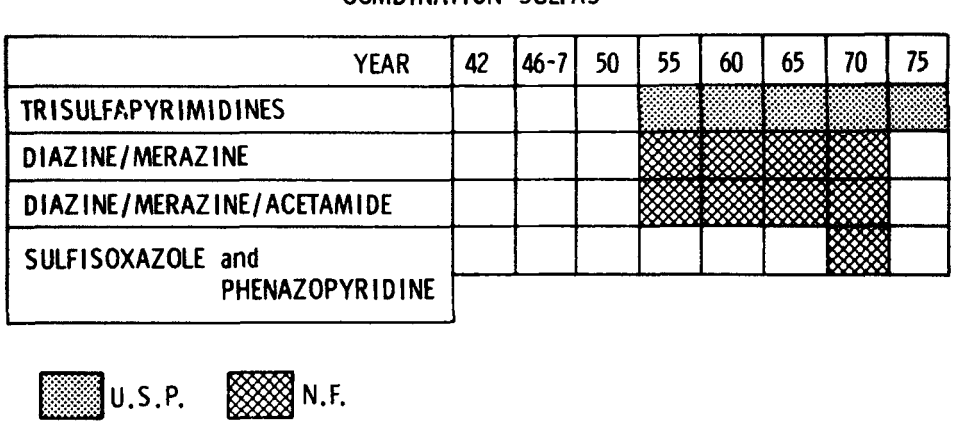


Fig. 8

reduced, although that factor is less noteworthy because the individual sulfapyrimidines already have a relatively low incidence. The last item in the figure illustrates the simple advantage of combining two different drugs with different activities in a single dosage form for greater convenience and reduced cost to the patient. The phenazopridine is included merely to reduce the burning sensation and pain in the urinary tract for which it has long been prescribed separately.

Penicillin-sulfa combinations used to be used widely, primarily for this same reason of convenience and economy, in administering two active drugs for additive effects, although there was actually some evidence of potentiation. Their marketing was with full FDA approval as to safety and effective-

ness. Later the approval was withdrawn for the reason of insufficient evidence as a fixed combination, and by that time no single manufacturer could afford the expense of producing such evidence, particularly with the advent of a broader assortment of antibiotics. But the FDA still permits the advocacy of using sulfas and antibiotics conjointly in certain severe infections. And the FDA recently approved a combination of a sulfa drug and trimethoprim for certain persistent or recurrent infections.

Going back to Figure 3 systemic sulfonamides, let us consider certain important questions which have been raised. Most of these drugs were discovered and developed in the laboratories of pharmaceutical companies. There are people who criticize the scope and methodology of industrial research. They say that once a "good" drug has been discovered by one company, others should not look for more effective or less toxic analogs or offshoots, but should direct their investigative activity to entirely different fields of therapeutic activity. But where would the critics have cut off the further investigation of new sulfa drugs?

Sulfathiazole was a "good" drug. Would they have stopped there? Or after sulfadiazine? Would they have accepted the risk of renal blockage as a necessary evil, without looking for further solutions? This line of questioning may seem academic

now, when sulfonamides are not often counted on for life-saving therapy. But it was pertinent 30 years ago for sulfas, and is still pertinent today for drug research in general.

The evolution of sulfonamide research and development was not limited to antibacterial drugs. The molecular modification process (which is still the principal way for chemists to move forward from the known to the unknown) had several kinds of fall-out, leading to the discovery of a number of important drugs in other fields of therapy.

One field involved carbonic anhydrase inhibition (Figure 9). Sulfanilamide had been known to produce acidosis, loss of fixed base, and rise in urinary pH. When it was shown to be a carbonic anhydrase inhibitor, a large number of analogs were prepared and tested. Out of this work acetazoleamide was developed and came into regular use. Ten years later two other compounds were added to the U.S.P.; all three are in the latest revision. For this kind of activity the SO_2NH_2 group of sulfanilamide must remain unsubstituted, whereas for antibacterial activity the other end of the sulfanilamide molecule--the para-amino group--remained unsubstituted. Carbonic anhydrase being broadly distributed in the body, these drugs are useful in epilepsy and glaucoma as well as for their diuretic effects.

CARBONIC ANHYDRASE INHIBITORS

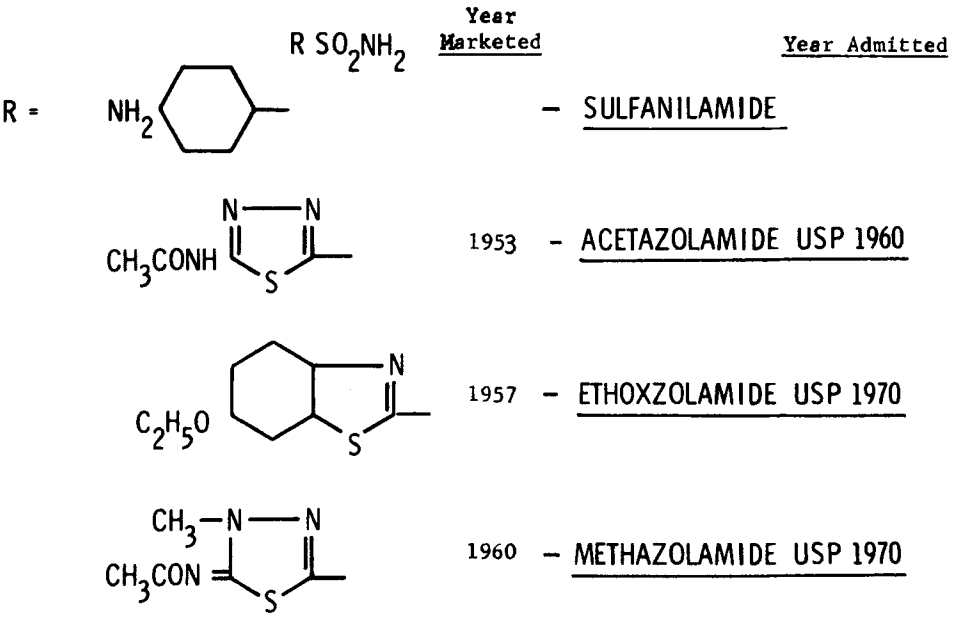


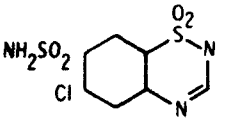
Fig. 9

Other diuretics having a free SO_2NH_2 group were discovered through other investigational approaches (Figure 10). Twelve of them are now official: the structures of the four U.S.P. compounds are shown. By much the same process of molecular modification, the observation that a certain antibacterial sulfathiadiazole had a blood-sugar-lowering effect led to the discovery and development of four antidiabetic agents currently in the U.S.P. (Figure 11).

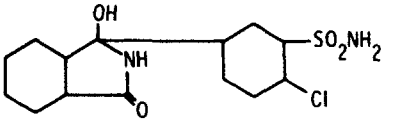
DIURETICS

Year Marketed

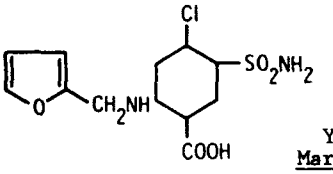
USP



– CHLOROTHIAZIDE 1960 195
(HYDROCHLOROTHIAZIDE USP 1960, 65, 70, 75) 195



– CHLORTHALIDONE 1970 197



– FUROSEMIDE 1970 1966

N.F.		Year Marketed			Year Marketed
	BENDROFLUMETHIAZIDE 1970	1959	BENZTHIAZIDE 1970		1960
	HYDROFLUMETHIAZIDE 1970	1959	CYCLOTHIAZIDE 1970		1963
	METHYCLOTHIAZIDE 1970	1960	POLYTHIAZIDE 1970		1962
	TRICHLORMETHIAZIDE 1970	1960	QUINETHAZONE 1975		1962

Fig. 10

In short, the synthesis and study of molecular modifications of known useful drugs has been most successful in producing more effective and/or less toxic drugs in the same therapeutic class as the prototype, and has led to the discovery of valuable drugs in new and unexpected areas.

But why are there so many different drugs on the market? The FDA merely pronounces a new drug safe and effective: why shouldn't it or some other authority give each drug a relative

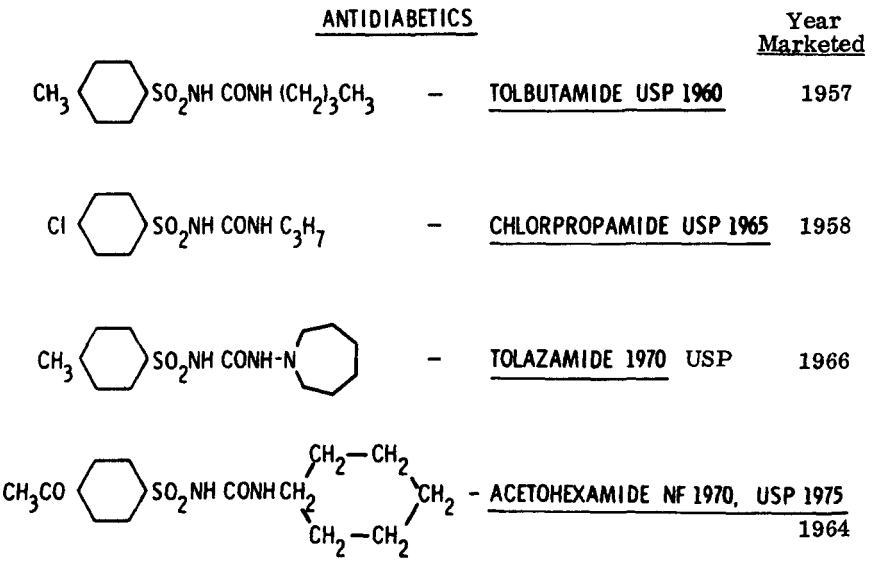


Fig. 11

efficacy rating, so that the practicing physician could be guided, or perhaps if necessary coerced, into prescribing only the "best" drugs? I once heard a serious proposal by a British health agency staff physician that a clinical comparison by made of all hypotensive agents to select the one which reduces hypertension most rapidly, and that the agency then require that that agent be used by physicians working under its auspices. The notion is patently ridiculous. But why wouldn't some guidance or direction by an authoritative group or agency be helpful? Could we start, perhaps, by ruling that only U.S.P. drugs be prescribed? If we did, patients would be deprived of the benefit

of new and improved drugs for ten years longer than they now have to wait. For that is the median time elapsed between original marketing and U.S.P. acceptance for the 69 therapeutic agents admitted for the first time in the 1970 revision. At the time of a drug's introduction into general use following FDA approval, it is impossible to predict the relative position it will deserve to attain with time and experience. The years of clinical study it has undergone at that time have been enough to justify the judgment that it is safe and effective, but by no means enough to indicate how it will stand the test of use by thousands of physicians in treating their patients. The U.S.P.'s policy from the beginning has been to list the "best-established" drugs, and I emphasize the word "established." Acceptance of a drug by the blue ribbon panel of physicians comprising the U.S.P. committee on scope is the final accolade to the drug's value, but it is based not only on the personal experience of the committee members but on the cumulative experience of thousands of trials in clinical practice following its release by FDA. I use the word "trials," because the efficient treatment of disease is experimental. The sound of that word is unpleasant, or even shocking, to unsophisticated laymen, because they don't understand it. They don't want themselves, or others, to be "experimented upon." They think that some paternal agency, preferably with

themselves as participants, should lay down rigid directives governing the choice of drugs. But "experimental" simply means a careful collection of all obtainable facts about the patient, a rational choice of a drug if indicated, in a rational starting dosage, and observation of the patient to see if the dosage needs to be changed or if another drug should be used in place of or in addition to the first one. For people vary so much in their response to drugs with respect to both desired and undesired effects (just as they do to alcohol) that a physician cannot know in advance whether a given drug in a given dosage will produce the desired result in a given patient.

It is for this reason that a multiplicity of similar drugs is necessary for optimum therapy. The 1964 edition of New & Non-Official Drugs discussing carbonic anhydrase inhibitors, said of methazolamide: "It is no more effective than acetazolamide; thus, its major usefulness is in the long-term treatment of patients who do not tolerate or respond to the older drug." Those are the crucial words: "tolerate" and "respond." That is why both drugs are now in the U.S.P., as well as a third--ethoxzolamide. That is also why the N.F. lists eight sulfonamide diuretics, in addition to the four listed in the U.S.P.

The same is true for other areas of drug therapy. Modell, in his prestigious "Drugs of Choice," 1970 edition lists 28 different

antihistamines and emphasizes that several drugs of this group should be tried at varying disages before concluding that antihistamines are ineffective in any given individual. He likewise lists 13 anticonvulsants useful in various types of seizures, and indicates the need for multiple drugs in that field of therapy with these words: One may begin with one or two drugs or in a severe case with three, but it is important to proceed slowly when increasing or decreasing the dosage as well as when adding or eliminating drugs."

The history of the evolution of sulfonamides, then teaches us that:

1) molecular modification of known drugs is a rational avenue of drug research whose practice has been most beneficial to public health.

2) a multiplicity of good drugs in a therapeutic class is indispensable to the optimum therapy of the individual patient.

3) restriction of the choices of the prescribing physician to a limited list of drugs arbitrarily dictated by third parties would be inimical to optimum care of patients and to the further progress of drug therapy.