DIAZOXIDE AND THE TREATMENT OF HYPOGLYCEMIA: AN HISTORICAL REVIEW

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This historical narrative on the antihypertensive hyperglycemic sulfonamide, diazoxide, really begins in the 1930's with studies of the antibacterial sulfonamides. Work by the I. G. Farben chemists, Mietzsch and Klarer, and the pharmacologist, Domagk,[1] resulted in the discovery that Prontosil (FIGURE 1) was an effective agent against streptococcal infections. Further work by a number of investigators[2-6] followed immediately, causing a flurry of excitement in therapeutics back in my own medical student days. Late in 1935, Trefouel and coworkers[2] at the Pasteur Institute discovered that sulfanilamide gave the same effect as Prontosil and that, indeed, sulfanilamide was the active moiety of the Prontosil molecule.

The toxicity of the sulfonamides was studied by a number of investigators[4,6-8] in the late 1930's. Even earlier (1930), Ruiz and colleagues[9] in a little-read Argentinian journal, reported several sulfonamide compounds as having a hypoglycemic effect. However, it was not until 1942 that Janbon,[10] at the University of Montpellier in France, reported the occurrences of grave, sometimes fatal, neurological disturbances in some patients with typhoid fever who were being experimentally treated with isopropylthiodiazole, a derivative of sulfanilamide. These symptoms were due to prolonged hypoglycemia. Loubatiéres,[11,12] in studies from 1942 to 1946, also at Montpellier, suggested the use of hypoglycemic sulfonamides in diabetes and described their mechanism of hypoglycemic action. He also found that some sulfonamides were hypoglycemic (FIGURE 1, middle row, left), some were hyperglycemic (FIGURE 1, middle row, right), and that others (not shown) had little or no effect on "blood sugar" levels.

Logically, those studies of the sulfonamides causing hypoglycemia were the first to be exploited, resulting eventually during 1954–1957 in highly useful agents in the treatment of diabetes after earlier agents had been found too toxic. Tolbutamide and chlorpropamide are representatives of this class.

In the meantime, other studies with sulfanilamide[8,13-15] eventually led to the synthesis of the first really useful oral diuretic, the carbonic anhydrase inhibiting acetazolamide.[16,17] This led in turn, in 1957, to the discovery of chlorothiazide (FIGURE 1), as synthesized at Sharp and Dohme – Merck, by Novello and Sprague,[18] and reported as an effective diuretic agent by Ford and coworkers,[19] Beyer and collaborators,[20] and Baer and coworkers.[21] This was a great improvement over the self-limiting diuretic activity of acetazolamide. However, it was demonstrated by Maren[22] that carbonic anhydrase inhibition was not the mechanism of diuretic action of chlorothiazide. Chlorothiazide was shown to have less than 0.5 percent of the carbonic anhydrase inhibition activity of acetazolamide by his *in vitro* test, being no more potent in this aspect than sulfanilamide.

Chlorothiazide began a new era of diuretic and, as it has developed, antihypertensive, therapy. Early in the use of chlorothiazide, Wilkins,[23] Finnerty,[24] and Goldner and coworkers[25] reported that this sulfonamide elevated blood glucose in certain susceptible individuals. These properties of the benzothiadiazine sulfonamides were quite difficult to pin down, and the published clinical studies of

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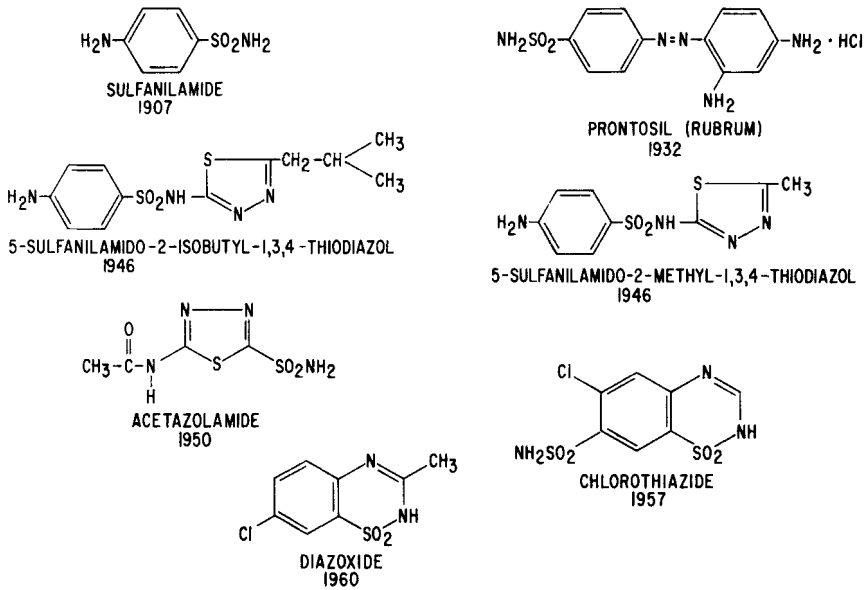

FIGURE 1. Structures of various sulfonamides including examples of antibacterial compounds (top two), hypoglycemic, R.P. 2256 (middle left), hyperglycemic, R.P. 2145 (middle right), diuretic (lower left), diuretic plus antihypertensive (lower right), and antihypertensive plus hyperglycemic (lower center).

that time were somewhat inconclusive. Newer techniques for insulin assay and a more potent hyperglycemic, diazoxide, have changed this picture (FIGURE 1).

Following the discovery of chlorothiazide and its antihypertensive properties, there was speculation about the mechanism of its antihypertensive action. At the American Heart Association Meeting in 1957, in discussion after his paper on the diuretic of chlorothiazide,[26] J. H. Laragh, commenting on his early studies on the effect of chlorothiazide in lowering blood pressure, stated that a diet containing less than 3 g of sodium chloride per day appeared necessary for effectiveness. Greater salt diets seemed to reverse this decrease in blood pressure. This was in line with the accepted thinking that such an antihypertensive effect could be shown with the diuretic mercurials. However, it was not accepted by all, including Hollander,[27] who felt that benzothiadiazine diuretics owed at least some of their antihypertensive activity to something other than saluresis. He showed that replacement of the salt and fluid loss did not bring the blood pressure back to previous values[28] (FIGURE 2), nor did salt-retaining corticoids re-establish the hypertension.

Rubin,[29] then in M. M. Winbury's Department at Schering Corporation, had already decided to test the hypothesis that benzothiadiazines that are not diuretic might reduce blood pressure. He used both the normal anesthetized dog and arterial strips to determine whether certain benzothiadiazines, which had been tested and set aside by Dick Taylor during the development of trichlormethiazide because they were nondiuretic, would, nevertheless, lower blood pressure. One of the early compounds he tested that satisfied the criteria of a nondiuretic hypotensive was diazoxide. The structure of diazoxide in FIGURE 1 shows that

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there is a striking similarity to chlorothiazide, with the sulfamyl group being absent.

In the early animal studies with diazoxide, Taylor[30] observed some initial sodium retention and potassium excretion in the dog. This was not marked at the doses tested and was not apparent when the 24-hour urinary output was measured, nor after administration for 21 days.

The distinct effects of diazoxide on sodium retention were found with the administration of the very first oral doses to man in metabolic studies. In M. M. Pechet's[31] studies (data in FIGURE 3), sodium retention was marked even over a 24-hour period with repeated doses. Incidentally, this patient simultaneously experienced a very good antihypertensive effect. The sodium retention was overcome by moderate doses of the same benzothiadiazine diuretic, trichlormethiazide, which had been successfully developed from Taylor's screen.

Thus, from the outset, it looked likely that diazoxide would have a stormy course as an oral antihypertensive agent. Even though it was effective as an oral antihypertensive in the early studies, it often caused edema and this action, presumably at least partly because of its salt-retaining effect, was somewhat unpredictable. However, during short-term intravenous administration, sodium retention was not a factor, and no diuretic was needed. This intravenous dosage form of diazoxide was made initially at my request: (1) for unequivocal demonstration in the clinic of antihypertensive action; (2) for metabolism studies; and (3) for studying hemodynamic effects. Intravenous diazoxide, rapidly administered, was immediately effective with minimal side effects. It is still being used with success in clinical investigations in acute hypertension.

Early in the clinical studies, it became clear that the hyperglycemia reported with chlorothiazide might also be a problem with diazoxide. Hyperglycemia was

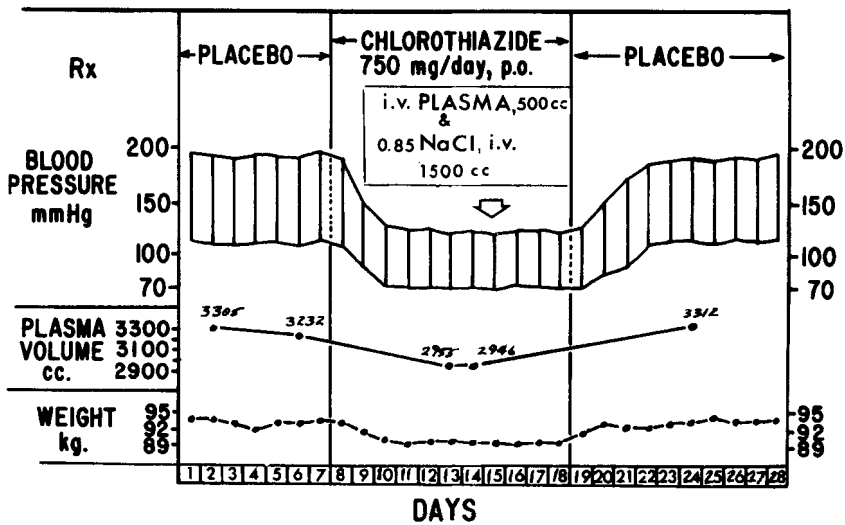

FIGURE 2. The relationship between antihypertensive and plasma volume effects of chlorothiazide. The reduction of blood pressure produced by chlorothiazide was associated with a reduction in plasma volume. When plasma volume was re-expanded to, and above, control values by infusing 500 ml of plasma and 1500 ml of isotonic saline, the antihypertensive effect of chlorothiazide was maintained. (Reproduced from Hollander, Chobanian and Wilkins[28] with permission from the authors and the New York Academy of Sciences.)

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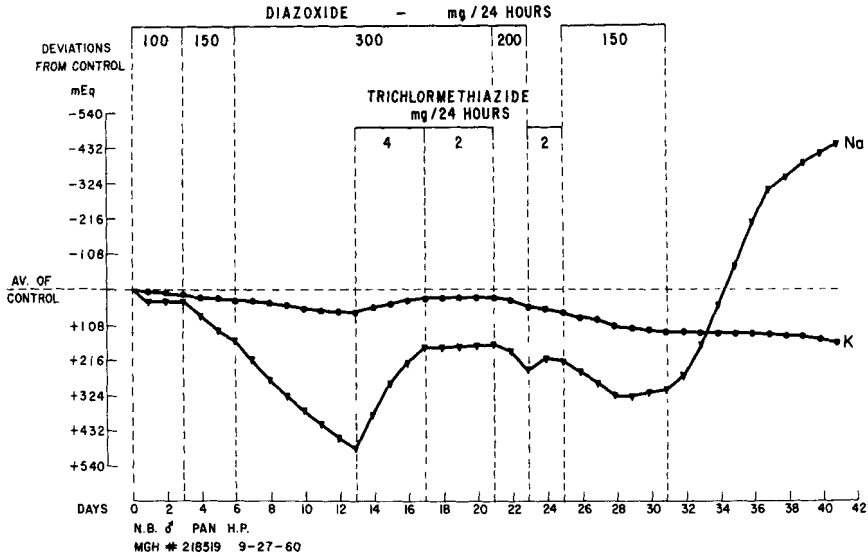

FIGURE 3. Data on cumulative K, Na Balances in a hypertensive, panhypopituitary male. (Reprinted by permission of M. M. Pechet, Harvard University, Boston, Mass., from his unpublished data.)

more likely to occur, it seemed, if the diazoxide was accompanied by a diuretic benzothiadiazine, often necessary to combat the salt retention and edema (TABLE 1).

At that time, October 1961, we already had evidence in dogs of an adverse synergistic effect of diazoxide and trichlormethiazide on glucose metabolism (FIGURE 4), and we reached the following conclusions:

1. Both diazoxide and trichlormetniazide can produce hyperglycemia in *susceptible* individuals.
2. The incidence of this effect is not great with either drug.
3. The two agents combined *may* be more diabetogenic clinically than either alone, but this is equivocal at the present time.

TABLE 1

EFFECT ON GLUCOSE METABOLISM IN APPROXIMATELY 150 PATIENTS TREATED AS OF OCTOBER, 1961

Conditions	Diazoxide (No. of Patients)	Diazoxide plus Trichlormethiazide (No. of Patients)
1. Known diabetes remaining controlled.	4	3
2. Known diabetes aggravated.	1	2*
3. Probable mild diabetes aggravated.	1	1
4. Hyperglycemia discovered while on therapy.	1	1
5. Questionable abnormality in glucose metabolism.	–	3

* One previously controlled on 4½ months of diazoxide alone.

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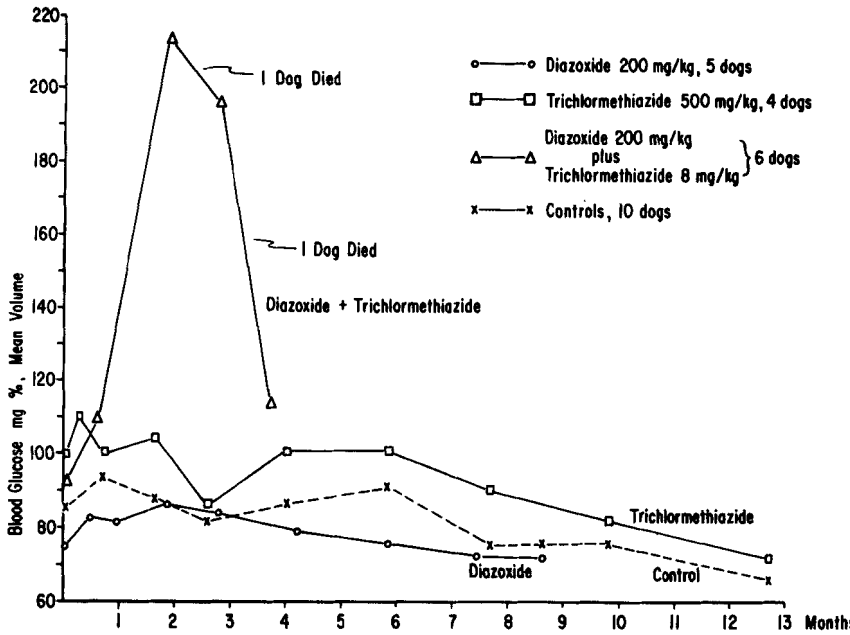

FIGURE 4. Composite toxicity studies in dogs using diazoxide alone, trichlormethiazide alone, and diazoxide plus trichlormethiazide. Control values are averages of all the control values obtained for both of the single drug studies.

We then recommended these steps for future investigation:

1. Investigators should be impressed with the possibility of glucose metabolism disturbances, especially with combined diazoxide and thiazide diuretic therapy.
2. Clinical pharmacology studies designed to clarify the diabetogenic effect should be carried out.
3. The apparent synergistic diabetogenic effect should be studied in dogs, and the mechanism of action should be investigated if the cause is not revealed by histology.
4. Promising diazoxide analogues should be studied in any animal screen emerging from "3".
5. A special consultant should be appointed.

By March, 1962, many of these steps had been carried out, including more definitive work on the toxicology of diazoxide and trichlormethiazide. Also, in clinical studies originally designed to determine the relative antihypertensive contribution of the diuretic alone and compare this with its use plus diazoxide, considerable attention was paid to glucose metabolism.

The toxicology studies in the dog, with 200 mg/kg of diazoxide and 8 mg/kg of trichlormethiazide (FIGURE 4), by Eggert[32] and his associates at Schering Corporation, had unexpectedly revealed remarkable adverse synergism. Hyperglycemia, ketoacidosis, and death occurred as early as eight weeks after the start of daily administration in some dogs. The same diazoxide dosage, given alone five days a week for one year, had caused no changes in fasting blood sugar,

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and even 500 mg/kg of trichlormethiazide alone had failed to affect the fasting blood glucose in dogs under similar circumstances.

This extraordinary adverse synergistic effect of the combination of these drugs on blood glucose was duplicated in controlled clinical trials using relatively much lower doses of each drug than in the dog studies (Marriot,[33] Okun and others[34]) (FIGURE 5). Note that trichlormethiazide alone caused no hyperglycemia, nor did it, in fact, affect glucose tolerance studies.

Adverse synergism was also noted in the mouse. During quality-control safety testing of a combination tablet in mice, the two agents combined were much more toxic than either agent given alone. Tabachnick[35] determined that these mice were dying primarily as a result of the hyperglycemic action of the diazoxide, which, he showed, would give this effect alone. This actually was the first time such hyperglycemic action was clearly delineated for diazoxide alone. Soon many investigators, besides Tabachnick,[36] were studying the mechanism of action of diazoxide hyperglycemia.[37–42]

The investigation of diazoxide for the treatment of hypertension was under critical review in early 1962. The accumulation of data on 275 patients who had been studied in the Phase 2 type clinical pharmacology studies at that time is shown in TABLE 2. A recommendation was made that, because of the undoubted and serious hyperglycemic effects seen in animals and in clinical studies (shown in Group B of TABLE 2) with the necessary combination of diazoxide and diuretic agents, the clinical studies should be discontinued.

Thus, it appeared that diazoxide was another good idea that did not quite work out. Due to the impending new Food and Drug legislation, everyone was anxious that problem drugs be discontinued. Considerable effort was required to keep diazoxide alive as an i.v. dosage form. Neither the sodium retention nor the hyperglycemic potential was a problem with this dosage form.

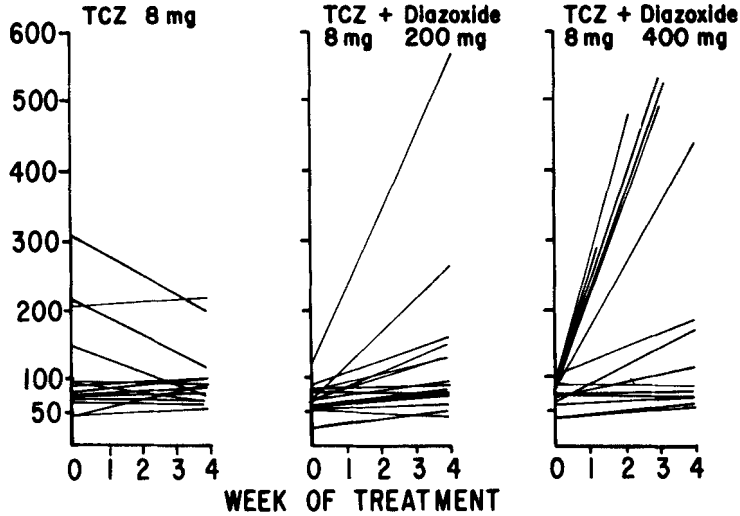

FIGURE 5. Individual blood-sugar courses of 45 hypertensive patients with oral trichlormethiazide (TCZ) alone and combined with diazoxide. (Adapted from Okun, Russell and Wilson. 1963. Arch. Internal Med. **112**: 882–88. Reprinted by permission of the authors and the Arch. Internal Med.)

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TABLE 2

SUMMARY OF BLOOD GLUCOSE ABNORMALITIES FOUND IN 275 HYPERTENSIVE PATIENTS TREATED WITH DIAZOXIDE ALONE OR DIAZOXIDE PLUS A THIAZIDE DIURETIC

Group	Classification	No. of Cases	% of Diabetics	% of Total (275)
A	Diabetes Uncovered or Aggravated by Diazoxide Alone	3	12	1.1
B	Diabetes Uncovered or Aggravated by Diazoxide Plus a Thiazide Diuretic	14	56	5.1
C	Diabetes not Aggravated by Diazoxide or Diazoxide Plus a Thiazide Diuretic	8	32	2.9
A, B, C	Total "Diabetics"	25	100	9.1

Dollery[43] reported in 1962 that hyperglycemia had occurred in two patients being treated for hypertension with diazoxide plus hydrochlorothiazide. He demonstrated suppression of insulin secretion, and proposed this as the mode of hyperglycemic action. Despite discussions at Schering Corporation of the possibility of diazoxide's being used for the treatment of hyperinsulinemic states, no clinical study was started owing to the probable narrow, therapeutic margin and the unfavorable climate existing for clinical investigation at that time. Almost two years elapsed after the above report before the first clinical studies were published.

In 1964, Drash and Wolff[44] reported the first test of the therapeutic effectiveness of diazoxide in severe hypoglycemia. They achieved a therapeutic triumph in a very sick child with severe leucine-sensitive hypoglycemia. This child is still receiving diazoxide and doing well, I believe.

A number of patients with a variety of diseases responsible for their hypoglycemia have now benefited from diazoxide therapy. TABLE 3 lists these in broad

TABLE 3*

ETIOLOGIC CLASSIFICATION OF HYPOGLYCEMIAS TREATED WITH DIAZOXIDE

Hypoglycemias	No. of Cases	Improved	Unimproved
1. Leucine Sensitive Hypoglycemia	16	15	1
2. Idiopathic Hypoglycemia of Infancy	20	16	4
3. Hyperplasia of Islets	2	0	2
4. Islet Cell Adenoma	27	24	3
5. Islet Cell Carcinoma	11	10	1
6. Extrapancreatic Neoplasms	11	8	3
7. Glycogen Storage Diseases (glucose-6-phosphatase deficiency) (debrancher deficiency) (hepatic phosphorylase deficiency)	4	4	0
8. Hepatocellular Disease	2	1	1
9. Hypopituitarism	3	1	2
10. Mushroom Poisoning	1	1	0
11. Insulin Overdose	1	1	0
12. Miscellaneous	5	5	0

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categories with an assessment of the improvement observed. While not in any way a cure for severe hypoglycemia, diazoxide appears to bestow very considerable benefit on the majority of such patients.

One should say a few words about side effects observed with diazoxide; these, while anything but trivial, are often worth the price, considering the malady. The side effects are similar to those seen in the clinical pharmacology studies with diazoxide in hypertension and reported in the literature on that subject. TABLE 4 lists the occurrences of various effects in the 103 cases of hypoglycemia in which I have previously cited the effectiveness of diazoxide. Perhaps two to three times that number make up the total of those treated, data being as yet incomplete in the others. Of these side effects, the one most frequent is hirsutism, first described by Conway of Michigan,[45] and also reported by Wilson of Iowa.[46] This phenomenon, while extremely disturbing to the hypertensive females in whom it occurred, was not noticed in the male in these early studies, which were limited in duration and extent. However, the clinical use of diazoxide for hypoglycemia in the young child has brought this side effect to the fore. The extent of it can be quite remarkable and disturbing. Yet, despite almost simian hirsutism in some of the children, we have been privileged to see that the parents did not ask for cessation of treatment, because the childrens' frequent hospital admissions for hypoglycemic convulsions had ceased. Instead of being stunted from the effects of cortisone, the children were growing nicely both mentally and physically. In original hypertension studies, the hirsutism was reported to me as disappearing five weeks after stopping the diazoxide.

The mechanism of the diazoxide hirsutism has, I understand, not yet been clearly delineated.

In summary, then, it has taken many years for this serendipitous sulfonamide saga to proceed in therapeutics from the antibacterial to the hypoglycemic to the diuretic to the hyperglycemic compound, and who can say that this is the end of the sulfonamide story.

In a different light, I think it worthy of mention that Dr. Kelsey, in her former role at the Food and Drug Administration, deserves a bouquet for her manner of handling the Investigational New Drug exemptions on the different indications for use of diazoxide. It gives hope that if good medical goals are followed without

TABLE 4*

SIDE EFFECTS OF ORAL DIAZOXIDE THERAPY; TOTAL NUMBER OF CASES — 103

Side Effects	No. of Cases
1. Hirsutism	25
2. Gastrointestinal intolerance (anorexia, vomiting, pain)	16
3. Edema	17
4. Tachycardia (supraventricular)	9
5. Postural hypotension	2
6. Hematological (neutropenia, eosinophilia, thrombocytopenia, anemia, lymphocytosis)	8
7. Dermatological (maculopapular rash, malar flush, photosensitivity)	4
8. Hyperuricemia (transient, asymptomatic)	11
9. Immunoglobulin decrease	4
10. Lymphadenitis	1
11. Gingival hyperplasia	1
12. Muscle wasting	1

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fear of censure, there will be less of the timidity that permits only the development of what is already obvious. Notwithstanding, "Primum non nocere," it is almost as much an abuse of the public to fail to develop a particularly useful agent as it is sometimes to treat unnecessarily and cause side effects.

Acknowledgment

The author acknowledges with thanks the assistance of Dr. C. H. Eades in the preparation of this manuscript.

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