LOWERED INCIDENCE OF SENSITIZATION THROUGH USE OF SULPHONAMIDE COMBINATIONS*

A NEW CONCEPT

BY

DAVID LEHR, M.D.

*Assistant Professor, Department of Medicine and Pharmacology, New York Medical College;
Assistant Attending Physician, Flower and Fifth Avenue Hospitals, New York City*

The incidence of allergic reactions is largely dependent upon the nature of the allergenic substance and the amount and concentration of the antigen to which the individual is exposed. It is also influenced by a great number of predisposing factors such as heredity, constitution, infection, immunization, dysfunction of various organ systems, as well as meteorological and geographical conditions. It is generally recognized that, within limits, the frequency of allergic reactions will increase in direct proportion with the intensity of exposure to the allergen,^{1 2 3} particularly in types of sensitization where the role of heredity is less marked. Apparently almost every individual can be sensitized by adequate contact.⁴

There should be little reason to doubt that this rule applies to all drugs that can act as full antigens or haptens, including the sulphonamides. Suggestions of a definite relation between dosage of sulphonamides and sensitization have been made repeatedly almost since the inception of their clinical application,^{2 5 6 7} and yet it is still widely believed that the incidence of allergic reactions from the sulphonamides is independent of the dosage used.^{8 9}

A critical evaluation of the vast literature on sulphonamide therapy, greatly enriched during the recent war by exacting large-scale studies of the armed Forces here and abroad, gives no support to the assumed independence of dosage and incidence of sensitization. Coburn,¹⁰ for instance, summarizing the tremendous programme of the United States Navy on "The Control of *Streptococcus hemolyticus*" with sulphadiazine, states that "sensitization did not appear to be produced by prophylaxis" even if used for as long as three to six months. His report deals with the experience gained on 600,000 men in approximately 3,000,000 man-weeks with a prophylactic dosage of 1 g. of sulphadiazine daily. The overall incidence of toxic reactions was 0.5% as compared with 4 to 8% of human subjects who develop reactions from therapeutic dosage of sulphadiazine. "Stopping prophylaxis during alternate weeks or alternate months was followed by no increase in the incidence of reactions. Subjects who did not react to the first course of prophylaxis were not sensitive to subsequent courses. The administration of sulphadiazine therapy to a large number of men who had previously tolerated prophylaxis did not cause reactions . . . There was no difficulty in obtaining a satisfactory therapeutic

effect from sulphadiazine in individuals who contracted streptococcal infections while receiving prophylaxis."

Similar points of view were expressed more recently by Rosenberg and Hench¹¹ from the Rheumatism Centre of the United States Army in their evaluation of sulphonamides for the prevention of rheumatic bouts. These authors, summarizing all reports published in the previous nine years, arrive at the following conclusion: "Theoretical considerations led certain investigators to fear that some patients, treated with small amounts of sulphonamides over long periods, might become 'sensitive' to these drugs and later be unable to take them for other therapeutic purposes. However, no such sensitization was observed. . . . Finally, there was some concern that virulent drug-fast strains of haemolytic streptococci might result from prolonged sulphonamide prophylaxis; no such eventuality has been reported."

It is the purpose of this discussion to demonstrate, with the help of data from the literature on sulphonamide therapy and our own experience with the use of sulphonamide combinations, that the incidence of allergic reactions is dependent upon the dosage of individual sulphonamides. It is further intended to show that the existence of a direct proportional relationship between dosage and production of sensitization may open a rational approach to the diminution in the incidence of drug allergy.

Dosage of Sulphonamides and Incidence of Drug Rash and Fever

In our search of the literature for comparative percentages of sensitization with small, medium, and large dosages of sulphonamides, particular attention was given to sulphanilamide, sulphathiazole, and sulphadiazine because these three drugs have been used most extensively since their introduction into therapy twelve, nine, and eight years ago, respectively, and therefore offer the richest source of comparative clinical data. One can reasonably expect that the findings for these sulphonamides will apply in like manner to other derivatives of the series.

It was realized from the start that clear-cut information could not be expected from so ambiguous and confusing a manifestation of sulphonamide toxicity. The so-called sensitization reactions actually lack any strict standards of evaluation, giving wide leeway to individual opinion and interpretation. It seemed of advantage, therefore, to limit the accounting of allergic reactions to "drug fever" and "rash," which are considered to represent the most common

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indicators of sensitizations. The reservation must be made, however, that the truly allergic nature of these reactions was established by subsequent testing in exceptional instances only. Without such tests drug fever may often be confused with a flare-up of the original disease and many non-allergic skin reactions may be counted as sensitization. This fact seems to have been disregarded by many authors, who consider every rash as sulphonamide allergy and therefore an absolute indication for the interruption of therapy. Otherwise, it is contended, more dangerous signs of sensitization such as hepatitis, "chemotoxic" nephritis, or agranulocytosis may be induced. In this connexion it should be remembered that the allergic nature of these serious but fortunately rare manifestations of toxicity has not been established. In fact, especially with regard to the haematopoietic system, much evidence was presented in favour of a direct and primary tissue toxicity¹² or a depletion of certain essential metabolites or vitamin factors.¹³

A detailed discussion of the pros and cons of allergy versus primary tissue damage is beyond the scope of this paper. It should be pointed out, however, that the intentional omission of extremely rare reactions of disputed nature from this account of sulphonamide allergy will not distort the values to any extent. It should also be clear that such data as can be obtained from the literature on rash and fever undoubtedly contain an appreciable number of non-allergic reactions. Hence, in using the terms "rash" and "fever" interchangeably for sensitization or allergy throughout this discussion I am fully aware of an unavoidable inaccuracy. The figures for true sensitization are probably lower.

An attempt was made to collect data from exacting reports with large groups of patients only; however, no claim of an exhaustive survey is made. Unfortunately, many good therapeutic reports lack clarity in their figures for rash and fever. If these two reactions are listed separately, because either one may occur alone, it would seem imperative to indicate how often both reactions occurred in the same individual in order to avoid over-estimations when the total incidence of sensitization is calculated. In all such instances I chose to err on the conservative side by taking only the higher of the two figures rather than their sum and thus to present approximations of the minimum possible incidence. It will be realized in the course of the discussion that the lower figures obtained in this manner for therapeutic dosages tend to disfavor the concept for which these data were compiled. Whenever feasible, the findings of various authors were combined into larger groups. The final data obtained in this manner are summarized in the accompanying Table.

Drug	Daily Dosage in Grammes	Days of Treatment	No. of Cases Treated	Incidence of Rash and Fever	References
Sulphanilamide	1-2	120-240	188	1.0%	15-17
	1.5-4	7-21	1,687	0%	18
	6-9	5-10	1,407	>10.0%	19-20
	Routine therapy*			7.2%	14
Sulphathiazole	2-4	3-15	3,584	0%	21-26
	6	3-10	2,475	>6.4%	19, 27-33
	6-10	5-10	529	>10.0%	6, 19, 34
	Routine therapy*			11.2%	14
Sulphadiazine	1	12-90	664,840	<0.5%	35-41
	2-4	3-20	18,185	0.07%	42-45
	4-6	7-14	500	1.8%	46
	6+	2-31	2,791	2.3%	27, 30, 42, 47-52
	Routine therapy*			2.9%	14

* These figures are based on a comprehensive compilation of the incidence of rash and fever reported in the literature.

For the purpose of correlation, the percentages of rash and fever recently published by Long¹⁴ for therapeutic dosages of the three sulphonamides were included.

The table clearly illustrates a definite relation between dosage and incidence of rash and drug fever. Sulphanilamide given in daily amounts of 1.5-4 g. for 7 to 21 days caused no sensitization in 1,687 patients, whereas 6-9 g. administered for only 5 to 10 days produced reactions in more than 10% of 1,407 patients. Even the worst offender, sulphathiazole, was tolerated without reaction by 3,584 individuals receiving 2-4 g. daily for 3 to 15 days, whereas signs of sensitization were found in more than 10% of 529 patients when full therapeutic dosages were administered for 5 to 10 days. Similarly, sulphadiazine when given in a daily dose of 1 g. to 664,840 men for 12 to 90 days resulted in less than 0.5% overall toxic reactions (with sensitization obviously on a much smaller scale). Even daily dosages of 2-4 g. continued for 3 to 20 days gave an incidence of only 0.07%. Approaching the routine dosage of 6 g. of sulphadiazine and more, the frequency of allergic reactions rises sharply to about 2.3%. The time factor seems less significant beyond the fact that a minimum of three to five days must elapse before allergic reactions begin to appear in any significant number.

These examples may suffice for demonstration of a definite correlation between the dosage of sulphonamides and the incidence of allergic reactions. It could be argued, with justification, that the smallest dosages were used in most instances for prophylactic treatment of healthy individuals, or at least of persons not suffering from acute infections, thus eliminating a possible contributory factor of sensitization. However, this does not apply to the 4 g. daily dosage of any of the three compounds used in the majority of instances for therapeutic purposes. In addition, it was also noted in sulphonamide prophylaxis that larger dosages result in a significant increase in allergic reactions.⁵³⁻⁵⁸ The high incidence of sensitization observed with a 6 g. daily dosage of any of the three sulphonamides could therefore not be explained solely on the basis of a difference in contributory factors. It would seem that any systemic sulphonamide can be administered in a dosage of 1-2 g. daily for long periods of time and even repeatedly^{15-17 36-41 53 54} in the same individual without the production of sensitization. The same drug in a dose of more than 4 g. in 24 hours, on the other hand, will induce allergic reactions in a definite and significant percentage of cases. The production of sensitization is apparently dependent upon the maintenance for some time of a certain minimum concentration of the allergen in the tissues which are to be sensitized.

This point of view is supported by many other clinical observations. First, the so-called "non-absorbable" sulphonamides like succinyl sulphathiazole (sulphasuxidine), even if given in large dosages by the oral route, will induce drug rash and fever rather infrequently.⁷ Blood levels from these compounds are seldom higher than 1-3 mg. (per 100 ml.). Sulphaguanidine, on the other hand, which is far better absorbed, is known to produce an appreciable incidence of drug rash and fever.^{7 59 60} In fact, Smith,⁶¹ who used massive dosages of this compound totalling 142 g. in a 10-day period, reported 21 instances of maculopapular rash among 44 *Shigella dysenteriae* carriers. Blood levels ranged between 10 and 14 mg. per 100 ml., which is unusually high for sulphaguanidine. The sensitization, incidentally, was specific for sulphaguanidine; rash was not produced by sulphathiazole, sulphadiazine, or sulphanilamide. Further evidence for the significance of high sulphonamide concentrations in the production of allergy seems to lie in the fact that sensitization reactions from

local sulphonamide application can be rather frequent^{7 62} and as a rule develop only at and around the immediate site of exposure (contact dermatitis), unless there was extensive systemic absorption from this local site.

There is a paucity of exact statements concerning the incidence of sensitization from topical application. Many reports on the use of sulphonamide ointments in pyogenic dermatosis⁶³⁻⁶⁸ do not mention the development of sensitization. Tate and Klorfajn,⁶⁹ on the other hand, reported 55 cases of sulphonamide dermatitis among 2,289 admissions to the skin department of a military hospital, and Darke⁷⁰ found 12 cases of dermatitis in 218 patients treated with sulphathiazole—an incidence of 5.5%. Northey⁷ estimates the average incidence of contact dermatitis from sulphathiazole as 2.2% and compares it with an incidence of 5% dermatitis medicamentosa from the oral administration of this drug.

The wide variations in the incidence of contact dermatitis reported by various authors are probably due in part to the differences in the type of infection treated and the duration of therapy, but are undoubtedly also influenced by the condition of the skin. In many instances the skin is largely intact; hence absorption is at a minimum and sensitization does not occur. However, the eroded areas of eczema, or skin denuded of its protective outer layers by burns or wounds, will permit of deep and extensive sulphonamide penetration. The result may be a high incidence of contact dermatitis.⁶² In fact, Lowell⁷¹ recently stated that "allergic reactions were so frequent and severe in eczematous areas of the skin that the prolonged use of sulphonamides on such sites has been cautioned against repeatedly." Systemic readministration of a sulphonamide to patients sensitized locally by previous topical application will often show exclusive or predominant reaction at the locally sensitized area.^{70 72-80}

Finally, the dependence of sensitization on absorbability and tissue concentration of sulphonamides can also be inferred from the excellent and exacting study of Sulzberger and associates⁶² on human volunteers. These authors investigated the "incidence of dermatitis following treatment with measured amounts of different sulphonamides in the same vehicle, on standard lesions (third-degree burns), in men of the same age group, living in the same environment, on the same diets, at the same occupation, and under similar experimental conditions." The overall incidence of dermatitis was found to be 19% in 254 men. The distribution of sensitization for the four sulphonamides employed was 57% for sodium sulphadiazine, 22% for sulphanilamide, 7% for sulphathiazole, and 5% for sulphadiazine. Based on these remarkable results the authors conclude that "the relative incidence of sensitization corresponded to the relative water solubility of the compounds—the most soluble giving the highest incidence of sensitization." It would seem, therefore, that, especially in systemic therapy, the production of sensitization could be avoided in many instances by preventing the rise of the tissue concentration of any one sulphonamide above a certain definite level. From the data compiled in the Table this tissue level is estimated to lie in the neighbourhood of 5 mg. per 100 ml., allowing for some variations with the different compounds of the series. In this connexion it should be pointed out that in sulphonamide prophylaxis (1 g. of sulphanilamide or sulphadiazine daily) blood levels range between 0.5 and 3 mg. per 100 ml.

However, the production of sulphonamide allergy should not be confused with the response of a sensitized individual in whom a single small dose may elicit a vigorous and typical reaction. It might well be that this fact has contributed to the mistaken conception that the production of

sensitization by sulphonamides may occur with small dosages as readily and as often as with full therapeutic amounts. According to Landsteiner's concept,⁸¹ sulphonamides should be considered as haptens or incomplete allergens which obtain the ability to cause sensitization by combining with tissue proteins. In line with this theory, sulphathiazole and sulphamerazine, which possess the greatest protein-binding power, cause high incidences of allergic reaction, although other factors undoubtedly are of importance. (It is known, for instance, that the thiazole ring is more apt to produce sensitization than the pyrimidine ring.) The complete allergen created by combination of a sulphonamide or its metabolite with protein may be highly specific. Individuals allergic to sulphathiazole often tolerate sulphadiazine or other derivatives of the series without reaction. The specificity is also expressed by the substantial difference in the incidence of sensitization reactions established for various sulphonamides. In the majority of human beings apparently the tissue cells are able to distinguish even between closely related sulphonamides with regard to their allergenic properties.⁸² In all such instances a combination of several sulphonamides in partial dosages should make it possible to exert full therapeutic effects and yet to "dilute" individual drug concentrations in the tissues below the level at which sensitization reactions are apt to occur. It is obvious that under these conditions the simultaneous presence of several distinct potential allergens in "non-antigenic" concentrations should be of little consequence.

If the cells of the body, on the other hand, do not distinguish between the various sulphonamides the danger of sensitization could still not be greater than if the full therapeutic dosage of a single sulphonamide had been administered. Obviously, the highest possible incidence will be determined by that drug in a combination which tends to induce allergic reactions most frequently. However, there should be no additive or even increased incidence of allergic reactions so long as individual sulphonamide concentrations are kept well below the level necessary for the production of sensitization to any one single sulphonamide in human beings with "normal" susceptibility. This concept seemed to be borne out by our experience with sulphonamide combinations.

Sulphonamide Combinations and the Incidence of Sensitization

Since 1944 unselected patients of all age groups suffering from acute bacterial infections have been treated with various combinations of sulphonamides at the Flower and Fifth Avenue Hospitals, as well as at the Metropolitan Hospital on Welfare Island. Adhering initially to the common belief that sulphonamide dosage is of little consequence with regard to the incidence of allergic reactions, we were on the look-out for an increase in sensitization.⁸³ Instead, however, we found a definite and significant decrease in the incidence of drug rash and fever, and no serious untoward reactions.⁸³⁻⁸⁶ Up to the present time more than 1,000 patients have received treatment with sulphonamide combinations at the hospitals associated with our institution. Although reports of allergic reactions in this series were sporadic on the whole, I have included for evaluation in the present paper only patients who were under my direct supervision or that of my immediate associates. Their number totalled 610. Of these, 393 were treated with a mixture of sulphadiazine and sulphathiazole, 160 underwent therapy with a combination of sulphadiazine and sulphamerazine, and 57 were treated recently with various combinations of three sulphonamides. Equal partial amounts of the different sulphonamides were employed in all instances by the oral or subcutaneous route. Reactions

attributed to sensitization were observed in 11 cases, making it an overall incidence of slightly less than 2%. The distribution was as follows: sulphadiazine-sulphathiazole combination, 8 cases (2%); sulphadiazine-sulphamerazine combination, 2 cases (1.25%); sulphadiazine-sulphamerazine-sulphapyrazine combination, one instance of rash, apparently not allergic.

Four patients showing drug fever and/or rash were tested subsequently with small dosages of the sulphonamides to which they had been exposed. Two of these had developed allergic symptoms during therapy with the sulphathiazole-sulphadiazine combination; however, both proved to be sensitized only to sulphathiazole and not to sulphadiazine. A third patient showed no reactions while on intensive therapy with the sulphadiazine-sulphathiazole combination. Several days after discontinuation of therapy 4 g. of a combination containing sulphadiazine-sulphamerazine-sulphathiazole was administered for the purpose of an absorption-excretion study. Rash, fever, and general malaise were observed within a few hours after administration, clearing completely within 36 hours.

Subsequent testing with the separate sulphonamides in the above-named order revealed, as in the first two instances, sensitization only to sulphathiazole, whereas sulphadiazine and sulphamerazine were tolerated without reaction. Finally, a patient with brucellosis treated intensively with a combination of sulphadiazine-sulphamerazine-sulphapyrazine (blood levels of 12-20 mg. per 100 ml. free sulphonamide), in addition to intermittent intramuscular injections of streptomycin, developed a confluent maculopapular rash over the entire body in the fourth week of treatment. Temperature at that time was continuously subfebrile. The emergence of the eruption was not accompanied by malaise or a febrile reaction. All therapy was stopped and the rash disappeared within 48 hours with residual light pigmentation. At this stage 0.5 g. doses, first of the separate and then of the combined sulphonamides, were administered at 24-hour intervals. Finally, one intramuscular injection of streptomycin was given. All drugs were tolerated without reaction. Temperature fell to normal and the patient was discharged as cured.

It is obvious from these examples that two sulphonamides can be given simultaneously without the development of sensitization to both drugs. The fourth case illustrates that in many instances reactions may be counted as allergic without sufficient evidence for such a contention. Apparently the rash in this patient constituted a primary toxic response of the skin to intensive and prolonged exposure to sulphonamides or streptomycin. Dermatoses caused by hypersensitization should always be differentiated from toxic non-allergic dermatitis caused by overdosage or accumulation of a variety of agents.⁸⁷

It should also be kept in mind that sensitization to several or all compounds of the sulphonamide series (group allergy) may develop in some individuals from the use of any one single representative of this group of drugs.⁸² Obviously, if any such person develops group allergy during treatment with sulphonamide combinations it would not necessarily prove that sensitization to all components of the combination was elicited by their simultaneous administration.

The low overall incidence of rash and fever (2%) that we observed in our patients treated with sulphonamide mixtures speaks against a simple summation of such reactions by employing combinations of several sulphonamides in partial dosages. Otherwise we should have observed an incidence in the neighbourhood of 10%, since more than 400 of our patients received combinations containing sulphathiazole. Actually, then, our findings indicate

a significant reduction rather than an increase in the incidence of sensitization. The most plausible explanation seems to lie in the lowering of individual sulphonamide concentrations in the tissues beyond the critical level necessary for the production of allergic reactions. It will be remembered that this concept was postulated earlier in this paper on the basis of the experience of many authors with single sulphonamides.

For clinical purposes a daily dosage of 2 g. of any sulphonamide seems to lie safely below the amount that would produce sensitization, except in rare instances with special hypersusceptibility. Thus a combination of three therapeutically equivalent sulphonamides would allow a daily dosage of 6 g. at a substantially reduced risk not only of renal damage but also of sensitization. If this concept proves correct the introduction of more than three sulphonamides into a combination should further increase the safety of sulphonamide therapy.

Comments

The clinical use of sulphonamide mixtures, although widely accepted to-day on the basis of the protection afforded the kidney, is still too recent to permit any decisive statement on the question of sensitization. Our own limited experience would seem sufficient to disprove the contention of an increase in the incidence of allergy by the proper employment of combined sulphonamides. The concept of a reduced incidence, however, requires confirmation by other authors and with larger series of patients.

Of the few clinical reports on sulphonamide combinations which have been published thus far from other institutions,⁸⁸⁻⁹² only the one by Zeller, Hirsh, Sweet, and Dowling,⁹² reporting on the combined use of sulphadiazine and sulphamerazine in 75 patients with meningitis, attempts to demonstrate a possible increase of allergic reactions. Unfortunately, these authors arrive at conclusions which are not supported by their own results but are based on the fallacious interpretation of statistical data. Since their point of view is diametrically opposed to our concept, the evidence which Dowling and his associates present in support of their contention deserves close scrutiny.

One is struck by the unusual combined tabulation "drug fever and/or conjunctivitis, drug rash and/or conjunctivitis," which seems to attach undue significance to conjunctivitis alone as a sensitization reaction. Obviously the combined reporting of these three reactions makes it impossible to elucidate the exact position of conjunctivitis in the overall picture of reactions counted as allergic in nature. However, it seems reasonable to assume that the exceptionally high figure for sensitization reactions reported by Dowling and his co-workers for sulphadiazine (10%), which is in conspicuous contrast to all reports in the literature, is due to the inclusion of conjunctivitis as an allergic reaction.

Although conjunctivitis is seen occasionally during sulphathiazole therapy, it seems extremely rare from sulphadiazine and homologues.⁷ Plummer and Wheeler⁴⁷ reported one case of conjunctivitis among 1,357 patients receiving full sulphadiazine therapy without qualifying the nature of this reaction. Other authors reporting toxic reactions from sulphadiazine or sulphamerazine do not mention the occurrence of conjunctivitis. Dowling himself saw no conjunctivitis in 137 patients with pneumococcal pneumonia treated with sulphadiazine.⁹³ We have not observed any instance of allergic conjunctivitis in our large series of patients treated with sulphonamide combinations. Incidentally, no statement is contained in Dowling's report whether any attempt was made to establish the allergic nature of conjunctivitis, which is a well-known and frequent

concomitant sign of meningitis. Furthermore, Dowling *et al.* increased the dosage of the combination arbitrarily by "25 to 33%" above the generally accepted routine dosage of sulphonamides. Thus adult patients received 8-9 g. of the sulphadiazine-sulphamerazine combination daily, as contrasted with the 6 g. maintenance dose used by these authors in previous series with the separate compounds. Consequently each patient on combination therapy received an additional amount of at least 21 g. of sulphonamide in the average 10-day treatment period.

While the authors neither claim nor prove the necessity for such a substantial increase in dosage when using the sulphadiazine-sulphamerazine combination, they formulate their conclusions on the advantages and disadvantages of mixture therapy as if they had used the ordinary required dosage, and thus present an entirely misleading picture. Apparently based on the prevailing point of view that the incidence of sensitization is independent of dosage, Dowling and his associates attempt to demonstrate statistically significant differences between the sulphadiazine-sulphamerazine combination and the separate compounds with complete disregard of the fact that the combination was used in a substantially higher dosage range. If we assume that the tissue cells were unable to distinguish between sulphadiazine and sulphamerazine, then an 8-9 g. daily dosage of the combination which produced the highest blood levels should be expected to result in a higher incidence of allergy than either compound at a 6 g. daily dosage. Even if, on the other hand, sulphadiazine and sulphamerazine had acted as two distinct and specific haptens an excessive dosage of the combination could have obviously created sensitizing tissue concentrations for both sulphonamides. The median blood levels obtained by Dowling *et al.* (7.6 mg. per 100 ml. for sulphadiazine, 11.0 mg. per 100 ml. for sulphamerazine, and 14 mg. per 100 ml. for the combination) illustrate this possibility very clearly. In either instance an increase in the percentage of sensitization would not be surprising and would obviously not prove the point that these authors had tried to make. In this connexion it should be remembered that they did not report a statistically significant increase of sensitization with the sulphadiazine-sulphamerazine combination. In conclusion, then, the results of Dowling and his associates are explainable on the basis of the substantially higher dosage schedule of the combination and therefore carry no weight against the concept under discussion.

The recognition of a direct proportional relation between the dosage of individual sulphonamides and the incidence of allergic reactions poses many new questions which far exceed the scope of this limited discussion. To mention only a few, it should be investigated whether sulphonamides which are structurally less closely related (like sulphadiazine and sulphacetamide) are more apt to be distinguished by the cells of the body as specific allergens than isomers or homologues (sulphadiazine, sulphapyrazine, and sulphamerazine). A positive finding would obviously influence the selection of sulphonamides for use in combinations. Consideration should also be given to the possible diminution of toxic manifestations other than those due to sensitization or crystalline deposition in the kidneys.

Sulphapyridine, abandoned as too toxic in full therapeutic dosage in the United States, and sulphathiazole, under consideration for elimination,⁹⁴ should be re-examined in the light of this concept. Both are highly potent chemotherapeutic agents with an excellent record of efficiency, especially in pneumococcal and staphylococcal infections, respectively. The inclusion of either drug in partial dosage into triple combinations with sulphadiazine and sulphamerazine should lower the incidence of their untoward reactions to a substantial degree. In addition, the *in vivo*

antibacterial efficiency of such combinations should equal, if not surpass, that of any one single sulphonamide.

Finally, the investigation should be extended to include manifestations of sensitivity elicited by many other drugs. It is known, for instance, that the principal toxic reactions from thiouracil are granulocytopenia, leucopenia, drug fever, and dermatitis.⁹⁵ Recently Cookson and Staines,⁹⁶ reviewing four years' experience with thiouracil, stated that "most toxic effects were seen when the daily dose exceeded 0.1 g." They found a decline in the incidence with the use of smaller doses. A similar suggestion was made by Williams and Clute.⁹⁷ McGavack and associates⁹⁸ believe that the incidence of agranulocytosis from thiouracil can be decreased by avoiding excessive dosages. Others⁹⁵⁻⁹⁹ fail to find a dependence of the incidence of toxic reactions upon dosage within the therapeutic range. It seems important to point out that in these instances dosages varied as a rule within the fairly narrow range of 0.4 to 0.8 g. thiouracil in 24 hours. In this connexion it is interesting to note that propyl thiouracil, which is effective in one-third the dosage of thiouracil on a weight basis, causes only 1.6% toxic reactions as compared with 9% for the latter drug.¹⁰⁰ This substantially lower toxicity of the propyl homologue, which is quite generally agreed upon,¹⁰¹⁻¹⁰⁵ has been attributed to the appreciably lower dosage schedule of this compound.¹⁰⁶ It has also been established that many patients sensitized to thiouracil can be continued on therapy with propyl thiouracil¹⁰¹⁻¹⁰⁴ or methyl thiouracil⁹⁶ without showing any ill effects. These observations suggest the possibility of lowering the incidence of dermatitis and fever and other toxic reactions occurring under therapy with full dosages of any one compound of the thiouracil series by using appropriate combinations of several homologues in partial dosages. Generally speaking, it should be feasible to diminish the incidence of certain untoward reactions from many drugs by employing partial amounts of therapeutically equivalent drugs of different molecular structure in combination instead of the full dosage of any one compound.

Summary

Perusal of the extensive literature on sulphonamides reveals that, in the dosage range employed in human prophylaxis and therapy, the incidence of drug rash and drug fever increases in direct proportion with the dosage of absorbable sulphonamides.

At an oral dosage of not more than 2 g. of sulphonamide in 24 hours none of the compounds used at present appears to produce rash or fever in any significant percentage of cases even if used for prolonged periods and repeatedly in the same individuals.

The incidence of these reactions assumes significant proportions when the dosage is increased to more than 4 g. in 24 hours, and reaches even higher percentages with full therapeutic amounts of 6 g. or more in 24 hours, provided medication is maintained for a minimum of three to five days.

These observations indicate that the production of so-called sensitization reactions is dependent upon the repeated presence of certain critical tissue concentrations of a sulphonamide for a minimum period of several days.

In the majority of patients sensitization is specifically limited to the sulphonamide used for therapy. Hence the simultaneous administration of several sulphonamides in partial dosage should result in a reduced incidence of sensitization because it permits "dilution" of individual drug concentrations below the level necessary for the production of allergy.

Practical experience with combinations of two or three sulphonamides in 610 patients demonstrated a conspicuously low incidence of drug rash and fever at the full therapeutic dosage of 6 g. in 24 hours.

The significance of this finding and its possible bearing upon toxic reactions from compounds of the thiouracil series, and drug allergy in general, are discussed.

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