insufficient teeth is more indicative of lack of reparative care than of the amount of dental decay that they had had.

The English and Irish had had the greatest amount of dental decay, whereas the Negroes and Chinese had the least. This fact was not dependent on dental care, since the English had a great number of filled teeth and a small number of decayed teeth, whereas the Negroes had a large number of decayed teeth and few filled teeth. Three times as many selectees from Irish communities were rejected because of dental defectiveness as from Portuguese or Russian (Jewish) communities.

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IN VITRO ACTION OF SULFAMERAZINE, PHTHALYLSULFADIAZINE, PHTHALYLSULFAMERAZINE AND PHTHALYLSULFATHIAZOLE ON ENTERIC PATHOGENS

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THE sulfonamides have produced clinical results beyond expectation. These drugs were first directed against the septicemias, especially streptococcal and pneumococcal infections. The attention of investigators later centered on infections due to other bacteria, notably those of the pathogenic intestinal group. Relatively little work has been done on the direct effects of the sulfonamide drugs on intestinal bacteria and most of the available literature deals with their clinical effects. The preponderance of clinical studies is justified and is the most important consideration for both patient and practitioner.

In most conditions where the sulfonamides are employed, the blood level of the drug — usually administered by mouth — if kept at a satisfactory concentration for the desired time seems to be responsible for the beneficial effects. The ability of a drug to be absorbed from the intestine in an amount sufficiently high to maintain a proper blood level is especially noted in diseases where a septicemia or bacteremia is manifested. This is particularly true in infections with streptococci, pneumococci, meningococci and the like.

The situation is different when one considers the possible effects of these drugs in infections where the gastrointestinal tract is the main site of the disease or pathologic changes. In such cases one may differentiate two large groups of intestinal diseases: those in which bacteria responsible for the disease are restricted to the intestinal wall, no bacteremia occurring at any time and those in which, in addition to the local intestinal changes, a bacteremia occurs more or less regularly during certain stages of the disease. No discussion will be attempted of the question whether one has to deal in these cases with a primary bacteremia and a secondary localization in the intestinal wall, or whether primary localization occurs in the intestine and is followed by bacteremia.

In the first group, where bacteria are confined to the intestinal wall, the resultant diseases are caused by the different Shigellas or by *Vibrio comma*. In the group where bacteremia occurs regularly, they are produced by members of the typhoid-paratyphoid group, *Eberthella typhosa* and the Salmonellas. The infrequent intestinal infections with *Bacillus anthracis*, with the Brucellas, with *Pasteurella tularensis* and with *P. pestis* should theoretically be included in the latter group.

It is apparent that the effects of the drugs on these dissimilar groups of enteric infections must depend on entirely different qualities inherent in them. If the bacteria are restricted to the intestinal tract, it is more appropriate to choose drugs that have a slow rate of absorption and remain in the intestine in effective concentration. In the second group, drugs must overwhelm the bacteria in the intestine as well as in the general circulation. Here, a drug with good but not too rapid absorption should be chosen, or even a combination of two different drugs may be administered. One of these should be easily absorbed, thus combating the bacteria in the circulation, whereas the other should be poorly absorbed, thus acting on bacteria in the intestinal lumen and wall.

Aside from the problem mentioned in the preceding paragraphs, the action of the various sulfonamides on the separate pathogenic bacteria should be known in detail. Owing to mutual chemical affinities, even

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slight changes in the composition of a given drug may alter its effects on various bacteria; it may become more useful in the destruction of one bacterium and less useful in that of another. It is fully realized that any conclusions drawn from the following experiments can cover only one — and perhaps not the most important — part of the story. Investigations made in vitro enable one to determine the immediate effect of a given drug on a given bacterium, but do not decide which drug is most useful clinically in a given disease. The questions of rapid or slow absorption, of producing and maintaining an appropriate blood level and of the rate of drug excretion cannot be solved by test-tube studies.

Experiments of this type may, however, prove useful in cases where several sulfonamides of similar absorption rates are available. They may be especially useful when performed with those pathogenic bacteria that exert their principal or exclusive action on the intestinal tract. So far as the intestinal diseases are concerned, there is apparently no unanimity of opinion concerning which sulfonamides should be used in combating the particular pathogenic bacteria involved.

According to the literature, there is no doubt whatsoever that some sulfonamides are effective against the dysenteric infections. It seems, however, that in infections with bacteria of the typhoid-paratyphoid group the effects of such drugs are not proved, since some difference of opinion on the subject exists.[1-6] These doubts, together with other reasons, account for the preparation of numerous new sulfonamides in the hope of finding a new compound that will prove effective in cases in which the older drugs have failed. This is laudable work, and any opportunity to evaluate a new drug and to determine its worth against certain bacteria is most welcome. We are therefore indebted to Dr. E. L. Burbidge of Sharp and Dohme, Incorporated, Philadelphia, for supplying us with four new sulfonamides.

So far as we know, only one of these drugs, sulfamerazine, is under clinical investigation; a few reports of its use have already appeared.[7-15] A similar sulfonamide with two methyl groups, sulfamethazine, has been tested clinically by three groups of investigators, with results comparable to those obtained with sulfamerazine.[16-18] Nothing has as yet been published on the other three drugs. These preparations were obtained during studies on several older well-known compounds for their effects on various enteric organisms. References in this paper are restricted to in vitro studies made against the intestinal organisms.[19-28]

The opportunity has thus been given to compare the effects of the new drugs on certain bacteria with the effects of the older drugs from which they are derived. At the present time all that will be done is to state briefly what the in vitro effects of the new drugs are on representative species of intestinal bacteria. Perhaps this will serve to expedite clinical applications that may follow.

Materials and Technic

The chemical structures of the drugs at our disposal were as follows:

Sulfamerazine is sulfa-methyl-pyrimidine or 2-sulfanilamido-4-methylpyrimidine. It is monomethylated sulfadiazine, but has some characteristics peculiar to the specific compound. Tests show that it is more readily soluble, more quickly and more fully absorbed and less rapidly excreted than is sulfadiazine.[8]

Phthalylsulfamerazine is sulfamerazine to which a phthalyl radical has been added.

Phthalylsulfadiazine is sulfadiazine to which a phthalyl radical has been added.

Phthalylsulfathiazole is sulfathiazole to which a phthalyl radical has been added.

These drugs are crystalline white powders, sparingly soluble in water. Solutions were prepared in sterile nutrient broth. In no case was it possible to obtain clear solutions above a concentration of two per cent. Even at this concentration sulfamerazine and phthalylsulfathiazole did not dissolve readily unless the container was gently heated. In a few cases it was found necessary to heat the stock solution just before use because of a slight amount of sedimentation. It occurred to us that heating might increase the concentration of the drug to a slight extent, but we believed the increase to be negligible. We attempted to minimize this effect by preparing only small amounts of the drugs at a given time.

Since it is known that the solubility of sulfonamides in water — and consequently in nutrient broth — increases with a rising pH, working with strong basic solutions would have been advantageous. But the alkalinity of the solutions was limited by the fact that the medium had to be favorable for bacterial growth. It was decided to maintain a pH of 7.6 in all dilutions throughout the course of the experimentation, using a few drops of 10 per cent sodium hydroxide to aid solution of the drug and to obtain the proper reaction. Lower concentrations were prepared by diluting the 2 per cent solution with necessary amounts of nutrient broth at pH 7.6. Routine solutions were concentrations of 2.0, 1.5, 1.0, 0.50, 0.25, 0.10, 0.05, 0.025 and 0.010 per cent.

The following bacteria were tested in these series: *Escherichia coli*, *Eberthella typhosa*, *Salmonella paratyphi*, *S. schottmülleri*, *S. enteritidis*, *S. suipestifer*, *Shigella dysenteriae* (Shiga), *Shig. paradysenteriae* var. *Flexner*, *Shig. paradysenteriae* var. *Hiss* and *Shig. sonnei*. A standard loop of each bacterium was taken from a twenty-four-hour slant on agar, transferred into 5 cc. of nutrient broth (pH 7.6) and incubated for twenty-four hours. The degree of cloudiness after this period of time varied with each organism.

In order to have approximately the same number of bacteria in all tubes, the twenty-four-hour cultures were standardized with a nephelometer. The neph-

elometer tubes were originally standardized against a twenty-four-hour growth of *E. typhosa*. By plating out and counting the ten different strains, it was determined that the nephelometer reading for *E. typhosa* could be used as well for the standardization of the other nine organisms, the percentage of error being practically zero. Consequently, all twenty-four-hour broth cultures were standardized against a tube of the nephelometer corresponding to a count of 16,000,000 bacteria per cubic centimeter. Some slight errors are possible in this method of standardization, but it was thought certain that a few thousand bacteria more or less would in no way alter the results of the experiments. The findings obtained in the series later proved this assumption to be correct.

TABLE 1. *Sample Protocol.*

Organism: *E. typhosa* Protocol: 36
Drug: Phthalylsulfathiazole
Tubes inoculated: 2-2-43 Plates made: 2-3-43

Concentration of Drug	Cloudiness of Tubes	Dilution Used	Endo Plates Count Plate 1	Endo Plates Count Plate 2
%				
2.0	Clear	Whole	0	0
1.5	Clear	Whole	0	0
1.0	Trace (?)	Whole	60	0
0.50	Trace	1:1000	225	0
0.25	Moderate	1:2000	575	90
0.10	Moderate	1:2000	810	200
0.05	Heavy	1:4000	Innumerable	1220
0.025	Heavy	1:4000	Innumerable	1270
0.010	Heavy	1:4000	Innumerable	1230
None (control)	Heavy	1:4000	Innumerable	1250

A 1:100 dilution of each standardized suspension was made in physiologic saline solution just prior to use. One tenth of a cubic centimeter of this dilution was added to 0.9 cc. of the respective drug dilution, so that each tube always contained the same number of bacteria (16,000 per cubic centimeter). All tubes were incubated for twenty-four hours and read for degree of cloudiness. Following this, appropriate dilutions of the growth were plated out on Endo's agar. After a few preliminary trials it was learned which dilutions were satisfactory in order to obtain a countable number of colonies on the plates. One tenth of one cubic centimeter of the respective dilution was always plated out, two plates being streaked with the same glass rod. In this manner there was regularly obtained a countable number of colonies on at least one of the plates after incubating them for twenty-four hours. As a control, a similar amount of bacteria was inoculated into 0.9 cc. of broth and twenty-four hours later plated out in the manner described above. It was thus possible to discover by comparison any slight bacteriostatic effect of the drug concerned. A sample protocol is shown in Table I.

Experimental Results

The experimental findings are listed in Table 2. The percentage noted in each column reveals the lowest concentration of the respective drug that produced the indicated effect. Each figure represents the average of ten complete trials. Any differences that were found among the separate trials never exceeded one tube higher or lower in concentration and were exceedingly rare.

Discussion

Several results are apparent from Table 2.

Sulfamerazine is effective against *Esch. coli* in vitro in a concentration of 2 per cent; the other three drugs are bactericidal only at concentrations above 2 per cent. The same drug is bacteriostatic for this organism at a concentration of 0.1 per cent, whereas the others fall between 1 and 2 per cent.

Phthalylsulfathiazole is the best bactericide against *E. typhosa*, being effective at 1.5 per cent, and it is bacteriostatic at 0.5 per cent. The other drugs range in bactericidal power from 2.0 to over 2.0 per cent, and in bacteriostatic effect from 1 to over 2 per cent. The superiority of phthalylsulfathiazole over the other three drugs is fully evident.

Against *S. paratyphi* phthalylsulfathiazole is bactericidal at 2 per cent, with the other drugs going above that concentration. For bacteriostatic action, both sulfamerazine and phthalylsulfadiazine are effective at 1 per cent, whereas the others are effective above 1.5 per cent.

Sulfamerazine is the most effective bactericide against *S. schottmülleri*, killing at 2.0 per cent, and together with phthalylsulfathiazole is effective as a bacteriostatic agent at 1 per cent.

Sulfamerazine and phthalylsulfadiazine are equally effective as bactericides against *S. enteritidis* at 1.5 per cent. Together with phthalylsulfathiazole, all three are bacteriostatic at 0.1 per cent.

Against *S. suipestifer* the best bactericide is phthalylsulfathiazole (1.5 per cent). The best bacteriostatic agents are sulfamerazine and phthalylsulfadiazine (0.5 per cent).

TABLE 2. *Bactericidal and Bacteriostatic Action of the Sulfonamides on Various Intestinal Bacteria.*

Organism	Action	Sulfamerazine	Phthalylsulfadiazine	Phthalylsulfamerazine	Phthalylsulfathiazole
		%	%	%	%
Esch. coli	A	2.0	2.0+	2.0+	2.0+
	B	0.1	1.5	2.0	1.0
E. typhosa	A	2.0	2.0+	2.0+	1.5
	B	1.0	2.0	2.0+	0.5
S. paratyphi	A	2.0+	2.0+	2.0+	2.0
	B	1.0	1.0	2.0+	1.5
S. schottmülleri	A	2.0	2.0+	2.0+	2.0+
	B	1.0	2.0	2.0+	1.0
S. enteritidis	A	1.5	1.5	2.0+	2.0
	B	0.1	0.1	0.5	0.1
S. suipestifer	A	2.0+	2.0	2.0+	1.5
	B	0.5	0.5	2.0	1.0
Shig. dysenteriae	A	0.1	0.5	1.0	0.5
	B	0.05	0.1	0.1	0.1
Shig. paradysenteriae var. *Flexner*	A	1.5	1.0	2.0	0.5
	B	0.05	0.1	0.1	0.05
Shig. paradysenteriae var. *Hiss*	A	2.0	1.0	2.0+	2.0+
	B	1.0	1.0	2.0	1.0
Shig. sonnei	A	1.5	1.0	2.0	1.5
	B	0.5	0.5	1.5	0.5

A = bactericidal concentration (complete destruction of bacteria).
B = bacteriostatic concentration (partial inhibition of growth as compared with control tube).

Each of the various strains of Shigella differs with respect to the bactericidal and bacteriostatic actions of the four drugs studied. The Shiga strain is destroyed by sulfamerazine at 0.1 per cent, the same drug being effective as a bacteriostatic agent at 0.05 per cent. The Flexner strain is killed by phthalylsulfathiazole at 0.5 per cent; the same drug, and also sulfamerazine, are bacteriostatic as low as 0.05 per cent.

A concentration of 1 per cent phthalylsulfadiazine proved to be bactericidal for the Hiss and Sonne strains, but the highest bacteriostatic effects are equally divided among sulfamerazine, phthalylsulfadiazine and phthalylsulfathiazole. These three drugs are bacteriostatic for the Hiss strain at 1 per cent and for the Sonne strain at 0.5 per cent.

From the results obtained on four hundred experiments with these four drugs and by comparison with the eight hundred protocols already obtained on the older sulfonamides, the following conclusions may be readily drawn:

Sulfamerazine is better than sulfadiazine when used in vitro against *S. enteritidis*, *S. suipestifer* and the Shiga and Sonne strains of Shigella. Sulfadiazine is a better bactericidal and bacteriostatic agent than is sulfamerazine when used against *E. typhosa*, *S. paratyphi*, *S. schottmülleri* and *Esch. coli*. Both drugs have similar bactericidal and bacteriostatic effects on the Hiss and Flexner strains of Shigella. The addition of the methyl group to sulfadiazine therefore makes it more effective chiefly against the dysentery organisms, but weakens its actions against some of the others in vitro.

Phthalylsulfadiazine is better than sulfadiazine when used against *S. enteritidis* and the Hiss, Flexner and Sonne strains of Shigella, but the reverse is true when these drugs are used against *E. typhosa*, *S. paratyphi*, *S. schottmülleri*, *S. suipestifer* and *Esch. coli*. Both drugs are equally effective against the Shiga strain. The addition of the phthalyl radical to sulfadiazine makes it more effective for most of the dysentery organisms and for *S. enteritidis* in vitro.

Sulfamerazine is decidedly better as a bactericide and bacteriostatic agent than is phthalylsulfamerazine against *all* the organisms studied. The addition of a phthalyl group to this particular drug diminishes the effective action of the sulfamerazine in vitro.

Phthalylsulfathiazole has a better bactericidal action than has sulfathiazole when used against *E. typhosa* and the Flexner strain of Shigella; it is also a better bacteriostatic agent against *S. enteritidis*. As bactericides both are equally effective against *S. enteritidis*, *S. suipestifer* and *Shig. sonnei*. Against *Esch. coli*, both paratyphoid species and the Hiss and Shiga strains of Shigella, phthalylsulfathiazole is much weaker, both as a bactericide and a bacteriostatic agent, than sulfathiazole.

The tabulation indicates that the best bactericidal and the best bacteriostatic effects on each organism examined are not always produced by the same drug. It is also apparent that, at least in vitro, the addition of the phthalyl group serves some limited advantage with sulfadiazine and sulfathiazole against certain bacteria. It actually diminishes the effective power of sulfamerazine for all bacteria studied. This observation, of course, does not necessarily mean that the actions in vivo are also lessened by the addition of the phthalyl radical. Since the attached radical is easily split from various compounds,[29] it is most likely set free in vivo, so that the end effects may be identical with those produced by the simpler sulfonamides. This question can be answered only by animal experimentation.

The results were obtained by testing one strain only of each of the organisms, otherwise the technical work would have extended beyond the facilities at our disposal. Helmholz[30] has shown for *Esch. coli* that different strains of this organism exhibit different resistances against concentrations of the same drug in urine. Possibly by testing more strains of a single type of organism the results would have been slightly altered. Since some of the differences demonstrated were so striking and so constant, however, we believe that the results may be considered valid.

Summary

Four new sulfonamide drugs — sulfamerazine, phthalylsulfadiazine, phthalylsulfamerazine and phthalylsulfathiazole — were tested for their in vitro action on certain enteric pathogens.

From the results obtained, it is apparent that, as with the older sulfonamide compounds, the Shigellas are more susceptible to bactericidal and bacteriostatic action in vitro than are strains representative of other genera.

In certain instances, the new compounds were found to be more effective in vitro than the older compounds, whereas in others, the reverse was found to be true.

We are indebted to Miss Marian Land for technical assistance furnished during these studies.

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MEDICAL PROGRESS

HEMATOLOGY

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DURING war, research in subjects not directly connected with military medicine must naturally become greatly restricted. Because of this, publications in the field of hematology have been fewer in number, but many of these are of immediate practical value. In line with these new conditions, this year's review will be limited to a discussion of three subjects: blood transfusions and blood substitutes, hemorrhagic diseases and hemolytic processes.

BLOOD TRANSFUSIONS AND BLOOD SUBSTITUTES

The Russian Contribution

Bagdasarov[1] reviews the development of the Russian system of blood storage and distribution, in many respects the forerunner of the blood and plasma banks of today. Perhaps realizing the imminence of a new world conflict, the Russians in 1927 set up the Central Institute for Blood Transfusion in Moscow, with separate decentralized institutes in various cities. By 1932, eighty of these institutes were in active operation for the distribution of blood to the surrounding communities and for active research in methods for the preservation, administration and storage of fresh and cadaver blood. The Spanish Civil War served as a perfect setup for the clinical application of these studies. It was found that a mixture of citrate and glucose was a better preservative than citrate alone, that the universal donor could be used on a large scale in the front lines without further typing or cross matching, and that undue hemolysis in transportation could be prevented by the use of isothermic containers, which were best transported by the airplane rather than by truck or train. The use of plasma in Russia has lagged behind that in this country and Britain, perhaps because every available soldier and noncombatant at or close to the fighting zone has served as a volunteer donor. The red-cell mass, a by-product of plasma preparation (see below), has been routinely used in cases of severe hemorrhage. A somewhat mysterious note in Bagdasarov's review is that regarding "physiological balanced solutions," which contain a certain amount of plasma in an alcohol-and-glucose-solution base. This cocktail-like infusion is said to reinforce the vital processes, especially when the wounded patient suffers from disturbed hemodynamics not associated with severe blood loss and in septic cases. Although not strictly apropos, mention may here be made of the development by Bogomolets[2] of A. C. S. (anti-reticular cytotoxic serum), with spleen and bone marrow used as antigenic substances. The resulting serum injected in small doses is said to enhance greatly the immune activities of the reticuloendothelial cells and thus help such diverse conditions as frostbite, slowly

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