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ANTIBACTERIAL THERAPEUTICAL PREPARATIONS

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The present application is a continuation-in-part of my copending U. S. patent application Serial No. 198,503, filed November 30, 1950, for "Antibacterial Therapeutical Preparations," which in turn is a continuation-in-part of my copending U. S. patent application Serial No. 2,653, filed January 17, 1948, for "Antibacterial Therapeutical Preparations," now abandoned.

My present invention relates to antibacterial therapeutic preparations.

It is an object of my present invention to provide therapeutic preparations having entirely new ways of antibacterial action.

It is a further object of my present invention to provide therapeutic preparations having an intensified antibacterial action.

In accordance with my concept of "biostrategy," which will be more fully explained later, i.e. the application of strategic principles in warfare against microorganisms, I propose to use therapeutic preparations comprising a combination of sulfonamides and penicillin. Due to competitive absorption by the gastro-intestinal tract, the individual agents of this combination enter the bloodstream in succession and reach their highest blood concentration at different times after oral administration of said therapeutic preparations.

An example will explain the "bio-strategic" effect of my preparations:

A particularly preferred preparation according to my present invention consists of a combination of sulfadiazine, penicillin and sulfamerase as co-active ingredients.

If, after oral administration of this preparation, the sulfadiazine reaches its maximum blood concentration, the weaker strains of bacteria are killed, while the stronger survive by adapting themselves to sulfadiazine.

This adaptation consists of an altered cell metabolism within the microorganism specifically directed against a specific chemotherapeutic agent and essentially different with different agents. Such adaptation enables the microorganisms to survive in a given sulfadiazine concentration, but weakens them against any following, unexpected attack from another agent, which is entirely different in nature, and in antibacterial action.

At this moment, the penicillin reaches its maximum blood concentration and hits the surviving bacilli more destructively than if they were not previously adapted to sulfadiazine. This can be compared with military forces which have been trained for tropical warfare but are sent to the Arctic; they would be less able to resist the adverse climatic influences of the north than troops without such a preceding acclimatization to tropical conditions.

This phenomenon repeats itself later when the sulfamerezine has reached its maximum blood concentration: the few remaining microorganisms which survived the second, namely the penicillin attack by another adaptation, succumb to this unexpected third attack.

It is to be stressed that this new approach in chemotherapy is distinctly different from the conventional method of combined chemotherapy. This conventional way aims at continuous effective blood concentrations of two or more different agents. Such continuous effective concentrations are obtained not by simultaneous administration but by administration of the individual agents at different time intervals, e.g. of penicillin every 2 to 3 hours, sulfadiazine every 4 to 6 hours, sulfamerezine every 8 to 12 hours.

A further advantage of my new preparation is the prevention of drug-fastness and the synergistic effect of the compound. Though its three components enter the bloodstream in three successive waves, they are simultaneously present in the bloodstream for at least 2 hours.

All drug-sensitive bacilli can develop resistance to an individual bacteriostatic agent if they are repeatedly exposed to sub-effective concentrations of this agent. As a result of insufficient treatment many strains have already acquired drug-fastness. Drug resistance can be experimentally produced by exposing a culture of a certain bacillus to low and then steadily increasing concentrations of a bacteriostatic or bactericidal agent. I have found that a much lesser degree of resistance is acquired if a strain is exposed to increasing concentrations of two different bacteriostatic agents.

No resistance at all develops if several such agents including penicillin are used. This phenomenon is of major importance for the future of chemotherapy.

As to the synergistic effect of the combination of co-active ingredients: if it is assumed that the chemotherapeutic efficacy of each of the three agents alone is 1, the efficacy of the combination of two is more than 2, and the efficacy of the combination of all three is more than 3; in fact it proves to be far beyond 10 against certain microorganisms.

Summarized, the results and advantages of the new antibacterial therapeutic preparations proposed by me are manifold:

1. Microorganisms which would not be killed
by any of the three chemotherapeutic agents alone are killed by their combination;
2. Microorganisms which can be killed by each of the three components alone require much smaller amounts of the combined agents for ex-
termination, the required amounts are considerably smaller than would be expected if merely an additive effect would be operative;
3. As a result of the reduction of the total amount of antibacterial agents as set forth under 2, toxic effects of each individual chemotherapeutic agent are avoided;
4. The development of drug fastness, the most essential drawback in chemotherapy is pre-
vented;
5. Due to a true synergistic effect, the treatment with the combination is much more eco-
nomic;
6. Fewer daily doses are required, and disturbing night doses can be discarded; and
7. Single doses are effective in many infec-
tions such as pneumonia.

It should be stressed that it was not a priori to be anticipated that several anti-bacterial agents combined would under all circumstances be more effective than each individual agent of such a combination. On the contrary, it has been found that some antibiotics, if combined and administered simultaneously, cancel out their ef-
cfectiveness and have an anti-bacterial action which is far below the antibacterial action of each individual agent.

Actually, it has been found that penicillin taken with certain other antibacterial agents such as for instance chloramphenicol, substantially re-
duces the antibacterial action of penicillin; these agents seem to have mutually antagonistic rather than additive or synergistic effects.

Contrary thereto, I have obtained unexpected bacterial effects with a therapeutic preparation particularly for peroral administration comprising as essential co-active ingredients sulfadiazine, sulfamerazine and penicillin in the ratio of be-
tween 4,000 and 100,000 units of penicillin per each .1 gram of the total amount of sulfadiazine and sulfamerazine. It should be noted that the term “essential co-active ingredients” as used throughout the specification and claims is in-
tended to define in a composition containing sul-
famerazine and penicillin the total amount of sulfadiazine and sulfamerazine present in the composition and the amount of penicillin present in the composition in the ratio range set forth above; these ingredients within the indicated ratio range can be combined to produce the desired syner-
gistic effects, and presence of an excess of peni-
cillin, if any, in said composition will act mainly additively and will not increase the syner-
gistic effects and therefore such excess penicillin is not to be considered an "essential co-active ingre-
dient."

I have found that particularly good results were obtained with penicillin in the ratio of between 4,000 and 30,000 units of penicillin per each .1 gram of the total amount of sulfadiazine and sulfamerazine.

Still better results were obtained with penicill-
in in the proportion of between 10,000 and 20,000 units of penicillin per each .1 gram of sulfad-
iazine and sulfamerazine.

As sulfonamides, I use preferably sulfadi-
zine and sulfamerazine in substantially equal amounts; sulfadiazine for its quick absorption, sulfamerazine for its slow absorption and ex-
cretion. Sulfadiazine forms a rapid peak of blood concentration and a wave lasting for 4 to 6 hours, sulfamerazine forms a longer wave lasting for 8 to 12 hours.

My present invention will be further illustrated by the following examples. However, I wish to stress that my invention is not intended to be limited to the same:

Example 1
An antibacterial therapeutic preparation compr-
inising in combination as essential co-active in-
redients substantially equal amounts of sulfad-
azine and sulfamerazine as sulfonamides and penicillin in the ratio of 10,000 units of penicillin per each .1 gram of sulfonamides.

Example 2
An antibacterial therapeutic preparation compr-
inising in combination as essential co-active in-
redients substantially equal amounts of sulfad-
azine and sulfamerazine as sulfonamides and penicillin in the ratio of about 20,000 units of penicillin per each .1 gram of sulfonamides.

Example 3
An antibacterial therapeutic preparation compr-
inising in combination as essential co-active in-
redients substantially equal amounts of sulfad-
azine and sulfamerazine as sulfonamides and penicillin in the ratio of about 5,000 units of penicillin per each .1 gram of sulfonamides.

Example 4
An antibacterial therapeutic preparation in tablet form, each tablet composed of .25 gram of sulfadiazine, .25 gram of sulfamerazine and 50,000 units of penicillin.

Example 5
An antibacterial therapeutic preparation in tablet form, each tablet composed of .25 gram of sulfadiazine, .25 gram of sulfamerazine and 100,000 units of penicillin.

Example 6
An antibacterial therapeutic preparation in tablet form, each tablet composed of .50 gram of sulfadiazine, .50 gram of sulfamerazine and 50,000 units of penicillin.

Example 7
An antibacterial therapeutic preparation in tablet form, each tablet composed of .30 gram of sulfadiazine, .30 gram of sulfamerazine and 100,000 units of penicillin.

Example 8
An antibacterial therapeutic preparation in tablet form, each tablet composed of .30 gram of sulfadiazine, .30 gram of sulfamerazine and 100,000 units of penicillin.

Example 9
An antibacterial therapeutic preparation compr-
inising in combination as essential co-active in-
redients substantially equal amounts of sulfad-
azine and sulfamerazine as sulfonamides and penicillin in the ratio of 30,000 units of penicilli-
lin per each .1 gram of sulfonamides.

Example 10
An antibacterial therapeutic preparation compr-
inising in combination as essential co-active in-
redients substantially equal amounts of sulfad-
azine and sulfamerazine as sulfonamides and
penicillin in the ratio of 4,000 units of penicillin per each .1 gram of sulfonamides.

**Example 11**

An antibacterial therapeutic preparation comprising in combination as essential co-active ingredients substantially equal amounts of sulfadiazine, sulfamerazine and penicillin in the ratio of 65,000 units of penicillin per each .1 gram of the total amount of sulfadiazine and sulfamerazine.

**Example 12**

An antibacterial therapeutic preparation in tablet form, each tablet composed of .20 gram of sulfadiazine, .30 gram of sulfamerazine and 325,000 units of penicillin.

**Example 13**

An antibacterial therapeutic preparation comprising in combination as essential co-active ingredients substantially equal amounts of sulfadiazine, sulfamerazine and penicillin in the ratio of 100,000 units of penicillin per each .1 gram of the total amount of sulfadiazine and sulfamerazine.

**Example 14**

An antibacterial therapeutic preparation in tablet form each tablet composed of .20 gram of sulfadiazine, .20 gram of sulfamerazine and 500,000 units of penicillin.

In order to ascertain the efficiency of therapeutic preparations of the type proposed by me, I carried out tests to determine on the one hand the effects of my new preparation, and on the other hand to compare such effects with the results obtained by separate administration of the single agents of my new preparation.

In one of these tests, thirty-three children with clinical diagnosis of pneumonia were treated with a single oral dose of a combination of sulfadiazine, sulfamerazine and penicillin as co-active ingredients in tablet form. Each tablet contained 0.25 gm. sulfadiazine, 0.25 gm. sulfamerazine, and 40,000 to 50,000 units of potassium penicillin G. The lower dose of penicillin, 40,000 units per each 0.5 gm. of combined sulfonamides, was applied to ten cases, and the somewhat higher proportion, 50,000 units per 0.5 gm. of sulfonamides, to the rest of the cases.

Children weighing up to 10 kg. received 0.2 gm. of combined sulfonamides per kg. of body weight; children between 10 and 20 kg., 0.15 gm.; and children beyond 20 kg., 0.1 gm. of sulfonamides.

The proportion of penicillin in the combination of co-active ingredients was 8,000 to 10,000 units per each 0.1 gm. of combined sulfonamides. The medication was given one-half hour before or at least two hours after meals.

Of thirty-three children, one vomited the tablets and was eliminated from this group. Six children did not respond to this treatment within forty-eight hours. All of them were revealed by further diagnostic procedures not to be cases of pneumococcus pneumonia. Two cases had pulmonary tuberculosis, one primary atypical pneumonia, one staphylococcus empyema, one asthmatic bronchitis, and one bronchiectasis.

In the remaining twenty-six cases the diagnosis of lobar pneumonia or bronchopneumonia could be corroborated. Two of these cases were complicated with bilateral otitis and one with tonsillitis.

All twenty-six cases responded to the single dose of the three combined agents within four to twenty-eight hours, or an average of fourteen and eight-tenths hours. The average was only thirteen and three-tenths hours for sixteen children receiving the somewhat higher penicillin doses, as compared with seventeen and two-tenths hours for ten children receiving the lower penicillin proportion.

The temperature of most of these children was normal at the 8 a.m. reading following the day the medication was given and remained normal thereafter.

The results of this test are compared in the following table with the results of similar tests in which either only sulfadiazine or only penicillin or oral sulfadiazine with intermuscular penicillin were administered. The groups of patients subjected to the various tests were as far as possible fairly equal as to size, severity of the disease, sex, and racial distribution:

<table>
<thead>
<tr>
<th>Number of Cases</th>
<th>Modification</th>
<th>Dose</th>
<th>Average Duration of Pneumonia before Treatment (Days)</th>
<th>Defervescence within</th>
<th>Average Duration of Fever (Hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25...</td>
<td>Single oral dose of penicillin plus sulfadiazine plus sulfamerazine</td>
<td>0.1 to 0.2 gm. sulfonamides per kg. body weight plus 4,000 to 10,000 units penicillin per 0.1 gm. combined sulfonamides</td>
<td>3.1</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>25...</td>
<td>Single oral dose of sulfadiazine</td>
<td>0.15 to 0.2 gm. per kg. body weight</td>
<td>4.0</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>23...</td>
<td>Full course of oral sulfadiazine</td>
<td>0.2 gm. per kg. on first day, followed by 0.1 gm. per kg. daily</td>
<td>3.7</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>13...</td>
<td>Intramuscular penicillin</td>
<td>150,000 to 600,000 units daily for 3 to 6 days</td>
<td>3.1</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>20...</td>
<td>Full course of oral sulfadiazine plus intramuscular penicillin</td>
<td>0.5 to 0.1 gm. per kg. daily plus intramuscular penicillin for 3 to 12 days</td>
<td>3.6</td>
<td>5</td>
<td>11</td>
</tr>
</tbody>
</table>

This table clearly illustrates the superiority of single oral doses of the combined three agents according to my present invention over the administration of single oral doses of sulfadiazine alone. In the event of administration of tablets comprising all three agents, the average duration of fever was only fourteen and eight-tenths hours as compared with thirty-eight and four-tenths hours in the group of patients treated with single higher doses of sulfadiazine. Pneumonias complicated with otitis media did not respond to single doses of sulfadiazine, while in the present series complications responded promptly.

a single oral dose of a combination of sulfadiazine, sulfamerazine and penicillin as co-active ingredients in tablet form. Each tablet contained 0.25 gm. sulfadiazine, 0.25 gm. sulfamerazine, and 40,000 to 50,000 units of potassium penicillin G.
Moreover, in the group treated with my new therapeutic preparation, twenty-five of twenty-six children became afebrile within twenty-four hours, while in the group treated with one single dose of sulfadiazine, the majority became afebrile only after more than forty-eight hours.

The above table also includes a comparative group of pneumonias treated for two to eight days with repeated intramuscular injections of 150,000 to 500,000 units of penicillin daily. This group indicates that continued treatment with large parenteral doses of penicillin is not more effective than single oral doses of the three combined agents. The average duration of fever in the group treated with parenteral penicillin was about twenty-one and five-tenths hours as compared with fourteen and eight-tenths hours in the group treated with single oral doses of the three combined agents in accordance with my present invention.

The last group in the table represents a group of twenty children with lobar pneumonia or bronchopneumonia treated for three to twelve days with a full course of oral sulfadiazine and continued intramuscular injections of penicillin. The average duration of fever in this group was forty-one and eight-tenths hours as compared with fourteen and eight-tenths hours in the group treated with single oral doses of the three agents as proposed by me.

The third group of twenty-three children was subjected to a full course of oral sulfadiazine treatment. The dosage was .3 gm. sulfadiazine on the first day, followed for several days by doses of .1 gm. of sulfadiazine per kg. of body weight. The average duration of fever in this group was forty-one and ten-tenths hours as compared with fourteen and eight-tenths hours in the group treated with my preparation.

The combination of sulfadiazine, sulfamerazine, and penicillin as co-active ingredients for oral administration is not only suitable for the single dose treatment of pneumonia; it also can be given in repeated doses. A preliminary series of twenty children with tonsillitis, otitis media, laryngitis, scarlet fever, or pneumonia was treated with three doses a day of the same combination, for one to two days only. Treatment was started in all cases within twelve hours after the onset of the disease. The maximum dosage was .1 gm. of combined sulfonamides plus 8,000 to 10,000 units of penicillin per kg. of body weight per day, half of this amount being given as the first dose. Defervescence took place after from eight to thirty-three hours, or an average of twenty and two-tenths hours. Fever did not recur in any of these cases, and the clinical symptoms subsided promptly.

While I have described the invention as embodied in antibacterial preparations, I do not intend to be limited to the details shown, since various modifications and changes may be made without departing in any way from the spirit of my invention.

Without further analysis, the foregoing will so fully reveal the gist of my invention that others can by applying current knowledge readily adapt it for various applications without omitting features that, from the standpoint of prior art, fairly constitute essential characteristics of the generic or specific aspect of this invention and, therefore, such adaptations should and are intended to be comprehended within the meaning and range of equivalence of the following claims.

What I claim as new and desire to secure by Letters Patent is:

1. An antibacterial therapeutic preparation particularly for peroral administration, comprising as essential co-active ingredients sulfadiazine, sulfamerazine and penicillin in the ratio of between 5,000 and 20,000 units of penicillin per each .1 gram of the total amount of said sulfadiazine and sulfamerazine.

2. An antibacterial therapeutic preparation particularly for peroral administration comprising as essential co-active ingredients sulfadiazine, sulfamerazine and penicillin in the ratio of between 10,000 and 20,000 units of penicillin per each .1 gram of the total amount of said sulfadiazine and sulfamerazine.

3. An antibacterial therapeutic preparation particularly for peroral administration comprising as essential co-active ingredients sulfadiazine, sulfamerazine and penicillin in the ratio of about 10,000 units of penicillin per each .1 gram of the total amount of said sulfadiazine and sulfamerazine.

4. An antibacterial therapeutic preparation particularly for peroral administration comprising as essential co-active ingredients substantially equal amounts of sulfadiazine and sulfamerazine; and penicillin in the ratio of between 5,000 and 20,000 units of penicillin per each .1 gram of the total amount of said sulfadiazine and sulfamerazine.

5. An antibacterial therapeutic preparation particularly for peroral administration comprising as essential co-active ingredients substantially equal amounts of sulfadiazine and sulfamerazine; and penicillin in the ratio of between 10,000 and 20,000 units of penicillin per each .1 gram of the total amount of said sulfadiazine and sulfamerazine.

6. An antibacterial therapeutic preparation particularly for peroral administration comprising as essential co-active ingredients sulfadiazine, sulfamerazine and penicillin in the ratio of between 4,000 and 30,000 units of penicillin per each .1 gram of the total amount of said sulfadiazine and sulfamerazine.

7. An antibacterial therapeutic preparation particularly for peroral administration comprising as essential co-active ingredients sulfadiazine, sulfamerazine and penicillin in the ratio of between 4,000 and 30,000 units of penicillin per each .1 gram of the total amount of said sulfadiazine and sulfamerazine.

8. An antibacterial therapeutic preparation particularly for peroral administration comprising as essential co-active ingredients substantially equal amounts of sulfadiazine and sulfamerazine; and penicillin in the ratio of between 4,000 and 65,000 units of penicillin per each .1 gram of the total amount of said sulfadiazine and sulfamerazine.

9. An antibacterial therapeutic preparation particularly for peroral administration comprising as essential co-active ingredients sulfadiazine, sulfamerazine and penicillin in the ratio of between 4,000 and 65,000 units of penicillin per each .1 gram of the total amount of said sulfadiazine and sulfamerazine.

10. An antibacterial therapeutic preparation particularly for peroral administration comprising as essential co-active ingredients substantially equal amounts of sulfadiazine and sulfamerazine; and penicillin in the ratio of between 4,000 and 65,000 units of penicillin per each .1
gram of the total amount of said sulfadiazone and sulfamerazine.

11. An antibacterial therapeutic preparation particularly for peroral administration comprising as essential co-active ingredients sulfadiazone, sulfamerazine and penicillin in the ratio of between 4,000 and 100,000 units of penicillin per each .1 gram of the total amount of said sulfadiazone and sulfamerazine.

12. An antibacterial therapeutic preparation particularly for peroral administration comprising as essential co-active ingredients substantially equal amounts of sulfadiazone and sulfamerazine; and penicillin in the ratio of between 4,000 and 100,000 units of penicillin per each .1 gram of the total amount of said sulfadiazone and sulfamerazine.

HERMANN VOLLMER.

REFERENCES CITED

The following references are of record in the file of this patent:


