The antimalarial activity of the sulfonamides was described very soon after the discovery of these drugs. As early as 1940, a number of papers, such as those by Diaz de León (31-33), Hill and Goodwin (56), Van der Wielen (129), Coggleshall (18-20, 23), Niven (83), Chopra et al. (10-13), Menk and Mohr (81), Farrnad et al. (37-38), Sorley and Currie (118), Sinton et al. (117), etc., had reported on a somewhat variable success obtained with sulfonamides in experimental and human malaria. For a further 10 years, i.e., until 1950, there still existed some interest in this chemical group, as reflected in some important clinical trials, for instance those by Fairley et al. (36) and by Coatney et al. (16, 17). However, with the advent of more reliable synthetic antimalarials, chemotherapeutic work on sulfonamides with practical aims was almost dropped and rather remained limited to basic questions of more theoretical interest like mechanism of action, potentiation of the effect of other antimalarials of the folic-acid-antagonist group on experimental malaria, cross resistance, etc. This work is linked to renowned names such as Greenberg, Rollo, Goodwin, Bishop, Eyles and Coleman, Hitchings, etc.

Excellent cumulative reviews on sulfonamides and malaria have been made by Curd (27) in 1943, Findlay (42) in 1951, and Hill (58) in 1963. It is somewhat astonishing that no major work was carried out during the years from 1955 to 1963, i.e., during the period in which, thanks to the discovery of the so-called long-acting sulfonamides, a better knowledge of the pharmacokinetics of these drugs was obtained. It is now evident that many of the early contradictory reports regarding the antimalarial effect of sulfonamides, made during the initial years of the sulfonamide era, were due to the scanty information on the pharmacokinetics of these substances in man and in laboratory animals, a gap which led or misled, among other things, towards empirical and therefore not quite reliable dosage.

At present, the reported resistance of certain *Plasmodia* strains to some major antimalarials such as pyrimethamine, chloroquine and perhaps even quinine, and, on the other hand, the availability of some sulfones and sulfonamides with a very sustained action, have made it advisable to reexamine the possible value of these substances as an auxiliary tool for the management of malaria. It is most unfortunate that this logical interest is hampered by the reports on cases of Stevens-Johnson and Lyell syndrome, observed during the use of some of these substances.

The purpose of this short review is to summarize: a) the available infor-
mation on the effect of the sulfonamides on the different species and cycle stages of Plasmodia, b) their mechanism of action and its implications, i.e.: potentiation and resistance, and c) the trials so far carried out with the longest acting sulfonamide sulformetoxine, Ro 4-4393 *.

As it can be seen from Tables I to IV, the effect of the sulfonamides has been tested on the blood schizonts in most of the laboratory animal Plasmodia. They are considerably active against the blood schizonts of P. berghei, P. gallinaceum, P. knowlesi and P. falciparum and less or not active in the rest. The results obtained in cases of spontaneous or induced falciparum malaria have been almost unanimously positive although the onset of action of the sulfonamides is slower than that of the major antimalarials. This has precluded their use in the treatment of acute malaria. The results reported on malaria due to P. vivax are less uniform. Some authors find them to be effective here (although always less so than in P. falciparum), whereas others (35, 36, 51, 81, 93, 106) find practically no therapeutic activity. This may have been due to differences in the dosage or to the fact that the effects of different sulfonamides vary considerably (42). Very few investigations have been carried out with sulfonamides in cases of malariae and ovale malaria.

Sulfonamides have a definite causal prophylactic effect against certain Plasmodia such as P. knowlesi and P. gallinaceum (Table II). Regarding human malaria, the reports are rather scanty, but it seems that sulfonamides, at the doses tested, do not act as causal prophylactics (16, 17). The sulfonamides do not exert any effect on the gametocytes of the human types of malaria (Table III). In fact, they can even increase their number in the blood (41).

Fairley et al. in 1945 and Findlay et al. in 1946 reported that sulfamethazine rendered the gametocytes of P. falciparum incapable of developing in the mosquito (Table IV). However, Laing in his recent studies did not find such an effect with Fanasil (70). Further research on this subject is therefore needed. There is no information which would allow the assumption that sulfonamides possess any activity as secondary tissue schizonticides in human malaria. According to Bishop, exo-erythrocytic parasites are “relatively insensitive” to proguanil and sulfadiazine (7).

Mode of action of sulfonamides in malaria: It is paradoxical that the mechanism of action of sulfonamides, although not in all its details, is better known than that of most major antimalarials. Since the initial work by Maier and Riley (76), who proved in 1942 that the antimalarial effect of the sulfonamides is antagonized by p-aminobenzoic acid, a number of studies have been carried out, mainly by Greenberg, Goodwin, Rollo, Bishop, Hitchings, Thurston, etc. (6, 47, 49, 50, 59, 60, 101, 102, 127). Sulfonamides, biguanides and pyrimethamine constitute the group of the so-called folic-acid-antagonist antimalarials, i.e. “those antimalarials whose action has been considered to be concerned with interference with the synthesis of purines and pyrimidines via the PAB → folic acid → folinic acid system” (102). According to Rollo (Fig. 1), sulfonamides probably act on reaction A by simple metabolite competition, whereas biguanides and pyrimethamine act in a more complicated manner on reaction B. These analogies and differences between the mechanism of action of sulfonamides on the one hand and of the biguanides and pyrimethamine on the other entail a complex framework of possible reciprocal effects when two of these drugs are given together (potentiation) or in succession (cross resistance).

The possibility of cross resistance has been dealt with in several recent 

(*) Trade name: Fanasil Roche (also mentioned in the literature as sulforthomidine and sulforthodi-methoxine).
## Table I

**Blood schizonticidal activity**

Sulfonamides have been found active as blood schizonticides in:

<table>
<thead>
<tr>
<th>Parasite</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. berghei</em></td>
<td>29,57-58,82,94,98-100,124-125</td>
</tr>
<tr>
<td><em>P. gallinaceum</em></td>
<td>28,58,78,94,119,132</td>
</tr>
<tr>
<td><em>P. lophurae</em> (less sensitive than*</td>
<td>21,28,78,79</td>
</tr>
<tr>
<td><em>P. gallinaceum</em>)</td>
<td></td>
</tr>
<tr>
<td><em>P. fallax</em> (less sensitive than</td>
<td>103</td>
</tr>
<tr>
<td><em>P. gallinaceum</em>)</td>
<td></td>
</tr>
<tr>
<td><em>P. circumflexum</em> (less sensitive</td>
<td>77</td>
</tr>
<tr>
<td><em>P. gallinaceum</em>)</td>
<td></td>
</tr>
<tr>
<td><em>P. knowlesi</em></td>
<td>10-11,18-23,92,95</td>
</tr>
<tr>
<td><em>P. cynomolgi</em> (less sensitive</td>
<td>21-23,53,116</td>
</tr>
<tr>
<td><em>P. knowlesi</em>)</td>
<td></td>
</tr>
<tr>
<td><em>P. inui</em> (less sensitive than</td>
<td>20,21,23</td>
</tr>
<tr>
<td><em>P. knowlesi</em>)</td>
<td></td>
</tr>
<tr>
<td><em>P. falciparum</em></td>
<td>2,12-13,16,23,33,36-38,41,56,66-69,71,73,75,81,83,89,106,110,117,132</td>
</tr>
<tr>
<td><em>P. vivax</em> (less sensitive than</td>
<td>12-13,17,23,37-38,56,61,73,118,132</td>
</tr>
<tr>
<td><em>P. falciparum</em>)</td>
<td></td>
</tr>
<tr>
<td><em>P. malariae</em> (less sensitive</td>
<td>12-13,23,26,37,45,110,129,132</td>
</tr>
<tr>
<td><em>P. falciparum</em>)</td>
<td></td>
</tr>
</tbody>
</table>

Sulfonamides have been found inactive as blood schizonticides in:

<table>
<thead>
<tr>
<th>Parasite</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. lophurae</em></td>
<td>18</td>
</tr>
<tr>
<td><em>P. relictum</em></td>
<td>27,29,57,77</td>
</tr>
<tr>
<td><em>P. cathemerium</em></td>
<td>18,28,77,132</td>
</tr>
<tr>
<td><em>P. nucleophilum</em></td>
<td>77</td>
</tr>
<tr>
<td><em>P. vivax</em></td>
<td>35-36,51,81,93,106</td>
</tr>
</tbody>
</table>

**BEST CLASSICAL BLOOD SCHIZONTICIDAL DRUGS: 4-AMINOQUINOLINES**

**MEPACRINE, QUININE, PYRIMETHAMINE, PROGUANIL**

**OF THE ABOVE UNPRACTICAL FOR SUPPRESSION: MEPACRINE, QUININE**

**UNPRACTICAL FOR TREATMENT: PYRIMETHAMINE, PROGUANIL**
Causal prophylaxis

Sulfonamides have been found *active* as causal prophylactics in:

<table>
<thead>
<tr>
<th>Parasite</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. knowlesi</td>
<td>42</td>
</tr>
<tr>
<td>P. cynomolgi (less sensitive than P. knowlesi)</td>
<td>53</td>
</tr>
<tr>
<td>P. gallinaceum</td>
<td>15,24,28-29,41-43,112,130</td>
</tr>
<tr>
<td>P. cathemerium* (canary) (less sensitive than P. gallinaceum)</td>
<td>132</td>
</tr>
<tr>
<td>P. lophurae (turkey) (less sensitive than P. gallinaceum)</td>
<td>132</td>
</tr>
<tr>
<td>P. falciparum</td>
<td>117</td>
</tr>
</tbody>
</table>

Sulfonamides have been found *inactive* as causal prophylactics in:

<table>
<thead>
<tr>
<th>Parasite</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. falciparum</td>
<td>16,36,132</td>
</tr>
<tr>
<td>P. vivax</td>
<td>16,36</td>
</tr>
<tr>
<td>P. relictum</td>
<td>77</td>
</tr>
<tr>
<td>P. nucleophilum</td>
<td>77</td>
</tr>
<tr>
<td>P. cathemerium* (canary)</td>
<td>18,28,132</td>
</tr>
<tr>
<td>P. lophurae (chicks and ducklings)</td>
<td>18,28</td>
</tr>
</tbody>
</table>

* Some sulfonamides active; some others inactive

**BEST CLASSICAL CAUSAL PROPHYLACTIC DRUGS:** PROGUANIL AND PYRIMETHAMINE (P. FALCIPARUM > P. VIVAX)

**ACTIVE BUT NOT PRACTICAL:** 8-AMINOQUINOLINES
Table III

Gametocytocidal activity

Sulfonamides have been found inactive as gametocytocides in:

<table>
<thead>
<tr>
<th>Parasite</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. falciparum</td>
<td>14, 33, 36, 42, 70, 111</td>
</tr>
<tr>
<td>P. vivax</td>
<td>42</td>
</tr>
<tr>
<td>P. malariae</td>
<td>42</td>
</tr>
</tbody>
</table>

BEST CLASSICAL GAMETO CYTOCIDAL DRUGS: 8-AMINOQUINOLINES

ACTIVE ONLY IN P. VIVAX AND P. MALARIAE: 4-AMINOQUINOLINES, MEPACRINE, QUININE

reviews (7, 58, 107-109). Fig. 2 to 9 are a poor attempt to represent graphically the main observation of cross or coincidental resistance in experimental malaria due to Plasmodia berghei, gallinaceum, cynomolgi and knowlesi that have been reported. These figures make no claim to being complete or perfect since I may have missed some valuable reports. On the other hand, there are some minor discrepancies in the literature, undoubtedly due to differences in the techniques used for creating resistance and to the inevitable differences among the strains.

Nevertheless, with regard to any possible clinical application of sulfonamides (alone or combined with pyrimethamine) the most important facts about experimental cross resistance are:

1) Sulfonamide-resistant strains of some species of Plasmodia (e.g. P. gallinaceum) are usually also resistant to proguanil and pyrimethamine (7, 101).

2) Strains resistant to pyrimethamine and proguanil or its triazine derivative are generally not or only partially resistant to sulfonamides (85, 98, 101, 113, 115, 122, 126).

3) DDS-resistant strains are usually resistant to sulfonamides (8, 87-88, 90, 122).

4) Usually there is no cross resistance between sulfonamides or sulfones and antimalarials not belonging to the group of the folic-acid-antagonists. Frequently there is even some hypersensitivity (55, 63, 84-88, 91, 120, 122).
Table IV

Sporontocidal activity

Sulfonamides have been found active as sporontocidal drugs in:

<table>
<thead>
<tr>
<th>Parasite</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. falciparum</td>
<td>36, 42</td>
</tr>
</tbody>
</table>

Sulfonamides have been found inactive as sporontocidal drugs in:

<table>
<thead>
<tr>
<th>Parasite</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. falciparum</td>
<td>70</td>
</tr>
</tbody>
</table>

**BEST CLASSICAL SPORONTOCIDAL DRUGS**: PYRIMETHAMINE, PROGUANIL

**ACTIVE BUT LESS PRACTICAL**: 8-AMINOQUINOLINES

![Diagram](image)

*Fig. 1*

---

after Rollo (102)
Fig. 3: P. berghei resistant to 4-aminoquinolines. Cross resistance to other antimalarials. (The arrows go from the substance to which the strain has been made resistant to the substance tested.)
Fig. 4: P. berghei resistant to the group Proguanil-Triazine-Pyrimethamine. Cross resistance to other antimalarials. (The arrows go from the substance to which the strain has been made resistant to the substance tested.)
Fig. 5: P. berghei resistant to the group Primaquine.
Cross resistance to other antimalarials. (The arrows go from the substance to which the strain has been made resistant to the substance tested.)

- Resistance
- Slight resistance
- No resistance
- hypersensitivity
Fig. 6: *P. berghei* resistant to the group Quinine or Mepacrine. Cross resistance to other antimalarials.
(The arrows go from the substance to which the strain has been made resistant to the substance tested.)
Fig. 7: *P. gallinaceum* cross resistance.
(The arrows go from the substance to which the strain has been made resistant to the substance tested.)
Fig. 8:
P. knowlesi cross resistant to the group Pyrimethamine-Proguanil.
(The arrows go from the substance to which the strain has been made resistant to the substance tested.)
Fig. 9: *P. cynomolgi* cross resistance.
(The arrows go from the substance to which the strain has been made resistant to the substance tested.)

- **Chloroquine**
  - Resistance
  - Inconstantly reported resistance
  - No resistance

- **Quinine**
  - Resistance
  - Inconstantly reported resistance
  - No resistance

- **Mepacrine**
  - Resistance
  - Inconstantly reported resistance
  - No resistance

- **Sulfonamides**
  - Resistance
  - Inconstantly reported resistance
  - No resistance

- **Pyrimethamine**
  - Resistance
  - Inconstantly reported resistance
  - No resistance

- **Proguanil**
  - Resistance
  - Inconstantly reported resistance
  - No resistance

- **Guanii**
  - Resistance
  - Inconstantly reported resistance
  - No resistance
Now to potentiation. The fact that sulfadiazine and other p-aminobenzoic acid competitors with antimalarial activity are able to potentiate the action of proguanil against blood schizonts of *P. gallinaceum* has been known since the work by Greenberg in 1949 (47, 49-50). Proguanil and pyrimethamine do not potentiate each other (101). Later on, it was proved that the same applies if the sulfonamide is replaced by a sulfone and/or if proguanil is replaced by pyrimethamine (4-5, 101). A similar potentiation has in the meantime also been confirmed in experimental and human toxoplasmosis (34, 44, 59). In malaria, however, there had until 1963 been only a few tentative attempts to test the potentiating effect between sulfonamides and pyrimethamine in man (Hurly in 1959 (62); McGregor, Williams and Goodwin in 1963, (80). In 1964, DeGowin and Powell (30) showed that 2.0 g sulfadiazine daily for 5 days given concurrently with 50 mg pyrimethamine daily for 3 days cured 5 out of 6 volunteers infected with the Malaya (Camp) strain of *P. falciparum* resistant to chloroquine, hydroxy-chloroquine, quinacrine, chlorguanide, and pyrimethamine. Previous trials with the same doses of sulfadiazine and pyrimethamine given separately had not been successful.

One month later, in December 1964, Laing (67) reported on the first results of his study of the antimalarial effect of Fanasil (Ro 4-4393). This sulfonamide shows the longest period of elimination ever described in man. It has a half-life of 100 to 200 hours. (Sulfadiazine: 17 hours). This permits therapeutically sufficient blood levels to be maintained by weekly administration of low doses, either orally or parenterally. The slow elimination is not due to any intentional conventional modification of the basic molecule (e.g. N- acetylation) or to the pharmaceutical presentation (e.g. repository injection or late release tablet), but to the intrinsic structure of the basic molecule itself. Oral absorption of Fanasil is as rapid as that of the usual sulfonamides. These two properties, rapid absorption and slow elimination, together with the good activity it has shown in the usual chemotherapeutic experimental tests (96, 128), have justified extensive clinical trials with the substance in the common indications of the sulfonamides (1, 25, 64), with special attention to those in which single-dose treatment (e.g. meningococcal meningitis in epidemic developing countries (39) and long-term treatments e.g. leprosy (3), trachoma (40), systemic mycoses (74) are most indicated.

On the basis of the experience gained during clinical trials in the treatment of about 15,000 cases (some 100 of them treated continuously for several years) it can be stated that the tolerance of Fanasil is at least as good as that of the most highly reputed sulfonamides. The possibility of oral weekly administration makes Fanasil quite suitable for combined treatment with pyrimethamine.

The activity of Fanasil in experimental malaria has been studied by Richards (94) (Table V). Fanasil showed good antimalarial activity and a marked potentiation with pyrimethamine against pyrimethamine-resistant strains as well as against strains of *P. gallinaceum* and *P. berghei* resistant to pyrimethamine, triazone or chloroquine. The pyrimethamine-resistant strain of *P. gallinaceum* was somewhat less sensitive to the potentiating mixture (pyrimethamine + Fanasil) than the normal strain. However, the resistance factor was only 2 to 5, as compared with > 300 for pyrimethamine alone.

These results have been confirmed in their main lines by Brener (9). The optimum potentiating ratio in these chemotherapeutic studies seems to be in the region of 10: 1 (Fanasil: pyrimethamine) but the range appears to be very broad. Prophylactic single-dose treatment showed that Fanasil has the most prolonged activity among other long-acting sulfonamides and DDS.
Fanasil (20 mg kg x 7) and Fanasil - pyrimethamine (2.6 mg kg + 0.004 mg kg x 7) were also effective against infection produced by *P. gallinaceum sporozoites*. Treated chicks remained free from parasites for the duration of the experiment (35 days of observation), whereas the controls died within 17 days (94). It seems therefore that there may also be a potentiation of the causal prophylactic effect.

Treatment of acute malaria with Fanasil alone or combined with pyrimethamine:

a) *P. falciparum*: Laing (68, 71, 72), working in Amani, Tanzania, i.e. in an area where pyrimethamine resistance is known to occur, has reported the following results:

A total of 105 "semi-immune" Bantu Africans seeking treatment for fever were treated with one dose of Fanasil (1 g) alone (45 cases) or with one dose of 500 mg Fanasil in combination with 12.5 mg pyrimethamine (45 cases) or with one dose of chloroquine (200 mg i.m. or 600 mg orally) (15 cases) and thereafter a diagnosis of acute *falciparum* malaria was made by means of parasite counts from thick blood films. The results are shown in Table VI. In the group receiving Fanasil + pyrimethamine, asexual parasitemia was cleared in 88% of the patients within 48 hours compared to only 30% in the group receiving Fanasil alone. In another experience, two small children who had not responded to 50 mg DDS did respond to 250 mg Fanasil alone (69).

In an unpublished study carried out recently in Malaya. Laing (72) tried Fanasil alone or with pyrimethamine in 62 "semi-immune" patients suffering from acute malaria due to *P. falciparum*. The results are shown in Table VII. The treatment was considered to be a failure in those cases where asexual parasitemia was present on the seventh day of observation or where therapeutic intervention with another antimalarial drug was necessary in the interest of the patient. After a single dose of 1 g Fanasil given to 9 individuals there was one failure. Clearance of asexual parasitemia was somewhat slower than in African patients (average 3.1 days compared with 2.3 days). Various combinations of Fanasil (200 mg to 1 g) with pyrimethamine (25 to 50 mg) gave similar results in 53 patients (6 failures) with an average duration of parasitemia of 2.2 days. Among the few patients receiving the highest dose of 1 g Fanasil + 50 mg pyrimethamine there were no failures. 4 patients who had early recrudescences of parasitemia and febrile symptoms after treatment with chloroquine (1.5 — 2.0 g orally over 3 to 4 days in 3 adults and 0.280 g parenterally in a two year old girl) were also treated with a single dose of Fanasil + pyrimethamine (1 g Fanasil + 25 mg pyrimethamine for the adults and 250 mg Fanasil + 6.25 mg pyrimethamine for the child); three of the patients were "apparently cured" and one (an adult) to whom pyrimethamine was given 3 days prior to Fanasil showed no response to the dose of pyrimethamine, whereas after Fanasil scanty asexual parasitemia persisted for 7 days. Among 36 patients treated with 600 to 2,500 mg chloroquine there were 11 failures.

In Bangkok, Harinasuta (52) gave Fanasil alone or in combination with pyrimethamine or chloroquine to 66 patients (adults) with recrudescences after chloroquine-resistant acute *P. falciparum* malaria. The preli-
The antimalarial activity against drug sensitive and drug resistant strains of *P. gallinaceum* and *P. berghei*.

Results expressed as the level of drug which reduces the parasitemia to 50% of the untreated controls (ED$_{50}$) (Richards$^{94}$)

<table>
<thead>
<tr>
<th>Drug</th>
<th>ED$_{50}$ (mg/kg x 7 orally)</th>
<th>ED$_{50}$ (mg/kg x 7 orally)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P. gallinaceum</td>
<td>P. berghei</td>
</tr>
<tr>
<td></td>
<td>Pyrimethamine sensitive strain</td>
<td>Pyrimethamine resistant &gt; 300 x</td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>0.03</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>Sulphorthomidine</td>
<td>20.0</td>
<td>25</td>
</tr>
<tr>
<td>Sulphorthomidine + pyrimethamine</td>
<td>2.6 + 0.004</td>
<td>5 + 0.02</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
### Table VI

Average duration of asexual parasitaemia of *P. falciparum* and fever after treatment with Fanasil alone and in combination with pyrimethamine (Laing, Tanzania 71, 72)

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of Pats.</th>
<th>Failures*</th>
<th>Mean duration in days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Parasitaemia</td>
</tr>
<tr>
<td>Fanasil ** 1 g</td>
<td>45</td>
<td>7</td>
<td>2.3</td>
</tr>
<tr>
<td>Fanasil 500 mg *** + Pyrimethamine 12.5 mg</td>
<td>45</td>
<td>0</td>
<td>1.8</td>
</tr>
<tr>
<td>Chloroquine 200 mg i.m. or 600 mg orally</td>
<td>15</td>
<td>0</td>
<td>1.7</td>
</tr>
</tbody>
</table>

* Parasites still present in blood films on the 7th day or other drug required before the 7th day.

** Children up to 11 years received 250 to 750 mg

*** Children up to 11 years received 125 to 375 mg
Table VIII

Effect of Fanasil given alone or in combination with Daraprim or chloroquine to adult patients with chloroquine-resistant falciparum malaria (Harinasuta, Thailand)

<table>
<thead>
<tr>
<th>Drug regimen (single dose)*</th>
<th>No. of patients treated</th>
<th>Successes</th>
<th>Failures</th>
<th>Average duration of parasitemia + fever in days (excl. failures)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cured</td>
</tr>
<tr>
<td>Fanasil 1 g</td>
<td>16</td>
<td>9</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Fanasil 1.5 g</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Fanasil 250 mg + Daraprim 12.5 mg</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fanasil 250 mg + Daraprim 25 mg</td>
<td>15</td>
<td>10</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Fanasil 0.5 g + Daraprim 25 mg</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Fanasil 1 g + Chloroquine 1.5 g (in 3 days)</td>
<td>17</td>
<td>13</td>
<td>-</td>
<td>2</td>
</tr>
</tbody>
</table>

* except for chloroquine
** with a follow-up of less than 28 days

C.T.E. = complete temporary effect (clearance of asexual parasitemia with subsequent relapse)
P.T.E. = partial temporary effect (reduction not abolition of asexual parasitemia)
minary results are shown in Table VIII. On the basis of clinical response and duration of parasitemia, the best results were obtained with the following combinations: A) 1 g Fansil (single dose) + 1.5 g chloroquine in three days; B) 0.5 g Fansil + 25 mg pyrimethamine in a single dose. The latter has the practical advantage of being a one-dose therapy. Since duration of parasitemia is longer than that seen after chloroquine in chloroquine-sensitive cases, further trials are being carried out with higher doses of the combination Fansil + pyrimethamine.

Sensitivity to chemotherapy of seven strains of *P. falciparum* found in four Brazilian regions, in patients who did not respond satisfactorily to chloroquine, was studied by Lopes and Rodrigues da Silva (75) in 25 neurosyphilitic patient with blood-induced malaria. All seven strains showed resistance to the standard “field--test” dose (10 mg.kg of chloroquine recommended by WHO for preliminary selection of suspected chloroquine-resistant strains). Three of the seven strains turned out to be only partially chloroquine-resistant, since parasitemia disappeared after a higher dose of chloroquine (3 g in 3 days). The other four strains were considered as fully resistant to chloroquine; two of them were also resistant to pyrimethamine, and at least partially, to quinine. These two last strains (Po. and Po.), i. e., those fully or partially resistant to the three above mentioned major antimalarials, were sensitive to Fansil combined with pyrimethamine. As shown in Table IX, the therapeutic response (8 cases), however, took place rather slowly. Clinical response was achieved in 4 to 8 days, the trophozoites disappeared from the blood in 4 to 6 days and the gametocytes in about a month.

Almeida, Brazil, (2) has reported on the preliminary results of an extensive study being carried out in cases of spontaneous malaria. The patients are followed up for 6 days after receiving one of the three following treatments: Group A) 10 mg.kg chloroquine, 5 days later 10 mg kg chloroquine and 5 mg kg chloroquine on each of the 2 following days (total dose 30 mg.kg in 8 days). Group B) 40 mg/kg chloroquine in 4 days. Group C) 1 g Fansil and 50 mg pyrimethamine on the first day and 0,5 g Fansil on the following day. According to the preliminary results (197 courses of treatment in 178 patients followed), some cases of the groups A and B have shown recrudescences during the follow-up period. In the group C (14 cases already observed over 60 days) 4 cases became negative during the first day of treatment and the other 10 cases during the second one. All of them remained negative over the follow-up period.

Peringle and Lane (89), Tanzania, have reported on the results obtained with 250 mg Fansil in 9 schoolchildren who developed one or two clinical fits of *falciparum* malaria three to six months after the injection of the repository antimalarials cycloguanil pamoate, or DADDS, or both (Table X). By the fourth day after the dose of Fansil trophozoites had disappeared from the blood in all cases.

b) *P. vivax.* Confirming the results obtained by previous workers with older sulfonamides, Laing in Malaya also found *P. vivax* to be less sensitive to Fansil than *P. falciparum* (Table VII) (72). Out of 13 patients with acute *vivax* malaria treated with 1 g...
Therapeutic response to the association

Ro 4-4393 + Pyrimethamine

(Lopes and da Silva, Brazil)

<table>
<thead>
<tr>
<th>No. of patient</th>
<th>Ro 4-4393/2 + pyrimethamine</th>
<th>Clinical response</th>
<th>Parasitemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pft</td>
</tr>
<tr>
<td>18</td>
<td>500 mg + 50 mg 5 d</td>
<td>5 d</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>Idem</td>
<td>5 d</td>
<td>4</td>
</tr>
<tr>
<td>21</td>
<td>Idem</td>
<td>6 d</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>1 g + 50 mg 3 d</td>
<td>5 d</td>
<td>4</td>
</tr>
<tr>
<td>25</td>
<td>Idem</td>
<td>8 d</td>
<td>5</td>
</tr>
<tr>
<td>26</td>
<td>Idem</td>
<td>4 d</td>
<td>4</td>
</tr>
<tr>
<td>27</td>
<td>Idem</td>
<td>5 d</td>
<td>5</td>
</tr>
<tr>
<td>19</td>
<td>Idem</td>
<td>5 d</td>
<td>6</td>
</tr>
</tbody>
</table>

* under observation

Pft = trophozoites (P. falciparum)
Pfg = gametocytes (P. falciparum)
d = days
Results obtained with a single dose of 250 mg Fanasil in 7 patients having developed clinical falciparum malaria 3 to 6 months after the injection of a repository antimalarial (cycloguanyl pamoate, discetyldiaminodiphenylsulfone or both)

(Pringle and Lane, Tanzania)
Fanasil, 5 were failures. Out of 14 treated with Fanasil + pyrimethamine 2 were failures. However, on the average the parasitemia disappeared as quickly as in *falciparum* cases that responded. Higher doses should be tried in view of the fact that another investigator in Indonesia has obtained preliminary results in *P. vivax* which are at least as good as those he obtained in *P. falciparum* (61).

c) *P. malariae* and *P. ovale*. The scanty material available on these two species seems to indicate that they respond worse to Fanasil than *P. falciparum*, but that the association Fanasil + pyrimethamine is active.

**Suppressive treatment** with Fanasil alone and combined with pyrimethamine.

a) *P. falciparum*. The effect of single and weekly administration of Fanasil, pyrimethamine, and their combination on parasitemia due to *P. falciparum* in schoolchildren was extensively studied by Laing in Tanzania (66, 72). The results are summarized in Table XI. It seems that in schoolchildren doses as low as 125 mg Fanasil weekly were capable of suppressing asymptomatic asexual parasitemia in the great majority but not in all cases. No failures were seen when this dose (or even less) was combined with 6.25 or 12.5 mg pyrimethamine. Pyrimethamine alone was not effective since 38% and 18% of the children still had asexual parasitemia 7 days after one dose of 25 and 75 mg respectively. Even after 4 to 6 weekly doses of 25 mg pyrimethamine, 27% of the children were still positive.

In the same holoendemic area in Northeastern Tanzania, Prin-
Table XI

Effect of Fanasil and pyrimethamine given alone or in combination against pyrimethamine-resistant Plasmodium falciparum in semi-immune schoolchildren with a pre-treatment parasite incidence of over 25% (Laing, Tanzania 66,72)

<table>
<thead>
<tr>
<th>No. of children examined</th>
<th>Dosage</th>
<th>No. of children with trophozoites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fanasil alone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>176</td>
<td>500 mg/week for 4-6 weeks</td>
<td>2</td>
</tr>
<tr>
<td>140</td>
<td>250 mg/week for 8 weeks</td>
<td>1 (after 2 doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 (after 4 doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 (after 8 doses)</td>
</tr>
<tr>
<td></td>
<td>125 mg x 1</td>
<td>0 (1 P. ovale)</td>
</tr>
<tr>
<td>37</td>
<td>100 mg x 1</td>
<td>4</td>
</tr>
<tr>
<td>36</td>
<td>75 mg x 1</td>
<td>1</td>
</tr>
<tr>
<td>35</td>
<td>50 mg x 1</td>
<td>2</td>
</tr>
<tr>
<td>33</td>
<td>25 mg x 1</td>
<td>3</td>
</tr>
<tr>
<td><strong>Fanasil (F) + pyrimethamine (P)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>178</td>
<td>F 500 mg + P 25 mg once weekly for 4-6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>159</td>
<td>F 250 mg + P 12.5 mg/week for 8 weeks</td>
<td>0 (after 2 doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (after 4 doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 (after 6 &amp; 8 d.)</td>
</tr>
<tr>
<td>125</td>
<td>F 125 mg + P 12.5 mg x 1</td>
<td>0</td>
</tr>
<tr>
<td>54</td>
<td>F 100 mg + P 12.5 mg x 1</td>
<td>0</td>
</tr>
<tr>
<td>83</td>
<td>F 75 mg + P 12.5 mg x 1</td>
<td>0</td>
</tr>
<tr>
<td>39</td>
<td>F 50 mg + P 12.5 mg x 1</td>
<td>2</td>
</tr>
<tr>
<td>37</td>
<td>F 25 mg + P 12.5 mg x 1</td>
<td>4</td>
</tr>
<tr>
<td>39</td>
<td>F 125 mg + P 6.25 mg x 1</td>
<td>0</td>
</tr>
<tr>
<td>29</td>
<td>F 100 mg + P 6.25 mg x 1</td>
<td>0</td>
</tr>
<tr>
<td>33</td>
<td>F 75 mg + P 6.25 mg x 1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Pyrimethamine alone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>133</td>
<td>12.5 mg for 8 weeks</td>
<td>17 (after 2 doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19 (after 4 doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17 (after 6 doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16 (after 8 doses)</td>
</tr>
<tr>
<td>122</td>
<td>75 mg x 1</td>
<td>22 (18%)</td>
</tr>
<tr>
<td>123</td>
<td>25 mg x 1</td>
<td>47 (38%)</td>
</tr>
<tr>
<td>684</td>
<td>25 mg/week for 4-6 weeks</td>
<td>184 (27%)</td>
</tr>
<tr>
<td><strong>Untreated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>67</td>
<td></td>
<td>48 (71%)</td>
</tr>
</tbody>
</table>
Response of asymptomatic parasitemias occurring among children (previously injected with a repository antimalarial) to single doses of Fanasil or Dapsone

(Fringle and Lane, Tanzania)

<table>
<thead>
<tr>
<th>Drug and dose</th>
<th>Type of repository drug</th>
<th>Days since injection</th>
<th>No. of patients</th>
<th>Patients with trophozoites of P. falciparum before and after the &quot;super-treatment&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Before treatment</td>
</tr>
<tr>
<td>Fanasil 100 mg</td>
<td>Biguanide</td>
<td>150</td>
<td>57</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Sulfone</td>
<td></td>
<td>53</td>
<td>18</td>
</tr>
<tr>
<td>Dapsone 100 mg</td>
<td>Biguanide</td>
<td>182</td>
<td>59</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Sulfone</td>
<td></td>
<td>59</td>
<td>7</td>
</tr>
<tr>
<td>Fanasil 100 mg</td>
<td>Biguanide</td>
<td>254</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Sulfone</td>
<td></td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td></td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Dapsone 100 mg</td>
<td>Biguanide</td>
<td>254</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Sulfone</td>
<td></td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td></td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Fanasil 50 mg</td>
<td>Biguanide</td>
<td>305</td>
<td>29</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Sulfone</td>
<td></td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td></td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Dapsone 50 mg</td>
<td>Biguanide</td>
<td>305</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Sulfone</td>
<td></td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td></td>
<td>19</td>
<td>10</td>
</tr>
</tbody>
</table>

* in both of these cases the parasite density was extremely low
The untreated controls showed continuing *falciparum* parasitemia in 69 to 81% of the cases throughout the trial. Both regimens of Fanasil were found to be highly effective against asexual *P. falciparum* parasitemia as from the first week when all cases were negative. In the Fanasil groups, the highest incidence of children with trophozoites was 2% after 4 weeks (in the single dose group), whereas in the chloroquine group the incidence of positive cases was 5% after one week and progressively increasing to 16% after 4 weeks.

b) *P. malariae*. Shute and Dowling (110) also registered quite a high pre-treatment incidence of asexual parasitemia due to *P. malariae* during the surveys in the above mentioned Nigerian schools. The rates of positive cases before and after treatment are given on the extreme right of Table XIII which shows a rate of 10 to 15% prior to treatment, increasing to 19% after 4 weeks in the control group. This table also shows that the effect of chloroquine on *P. malariae* was entirely satisfactory and that both regimens of Fanasil were almost as effective as chloroquine.

Recent (unpublished) work carried out in Indonesia (61) indicates that Fanasil given alone or together with pyrimethamine is capable of completely suppressing *P. malariae* parasitemia by the second week after the first dose. Confirmatory trials are being undertaken.

c) *P. vivax* and *P. ovale*. The number of cases treated with Fanasil is too small to permit evaluation of the results. In Africa, Laing (72) observed the emergence of *P. ovale* in 2 patients having received weekly doses of 250 mg Fanasil. In another case trophozoites persisted after one dose of 1 g Fanasil. Shute and Dowling (110) observed persistence of *P. ovale* in 6 schoolchildren treated with Fanasil. In 3 further cases the trophozoites apparently emerged during suppressive treatment with Fanasil. In Indonesia, clearance of *P. vivax* parasitemia seems to have been rather slow, complete clearance having been achieved 3 weeks after the beginning of treatment with Fanasil, with or without pyrimethamine, given as a single dose or once weekly.

Gametocytocidal effect: According to the findings reported by Shute and Dowling (110) and by Laing (66, 72), Fanasil has actually no gametocytocidal effects, the slow disappearance of sexual forms of *P. falciparum* being the result of the schizonticidal action of the drug.

Effect on sporogony: Investigations were carried out by Laing (70, 72) to determine the effect of Fanasil alone and combined with pyrimethamine on *falciparum* sporogony. Batches of laboratory-bred *Anopheles gambiae* were fed on patients with sexual parasitemia after treatment. All surviving mosquitoes were negative after having fed on 2 patients previously treated with 500 mg Fanasil + 12.5 mg pyrimethamine. The same result was obtained in a further 2 patients after the combination of 500 mg Fanasil and 6.25 mg pyrimethamine. However, when a 1 g dose of Fanasil alone was given to a patient on two occasions, a significant number of mosquitoes were found to be positive after each dose. Consequently Fanasil alone does not seem to affect normal *falciparum* sporogony in mosquitoes. When given together with a small dose of pyrimethamine, which may be insufficient in itself, there appears to be potentiation of the sporontocidal effect of the latter. In experimental malaria (*P. gallinaceum*) such a potentiation has already been described by Ramakrishnan et al. (91) for DDS, although given by itself this substance did not show any sporontocidal effect.
<table>
<thead>
<tr>
<th>Drug and dosage</th>
<th>Blood surveys</th>
<th>No. of patients examined</th>
<th>P. falciparum</th>
<th>P. malariae</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive Rate</td>
<td>Rate %</td>
</tr>
<tr>
<td>Fanasil 500 mg once a week for 4 weeks</td>
<td>Before treatment</td>
<td>209</td>
<td>161</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>after: 1 week</td>
<td>195</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2 weeks</td>
<td>194</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>3 weeks</td>
<td>189</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>4 weeks</td>
<td>185</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Fanasil 500 mg single dose</td>
<td>Before treatment</td>
<td>261</td>
<td>175</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>after: 1 week</td>
<td>240</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2 weeks</td>
<td>237</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>3 weeks</td>
<td>238</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>4 weeks</td>
<td>233</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Chloroquine 300 mg single dose</td>
<td>Before treatment</td>
<td>248</td>
<td>185</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>after: 1 week</td>
<td>222</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2 weeks</td>
<td>216</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>3 weeks</td>
<td>223</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>4 weeks</td>
<td>147</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Untreated controls</td>
<td>Before trial</td>
<td>78</td>
<td>60</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>after: 1 week</td>
<td>89</td>
<td>61</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>2 weeks</td>
<td>76</td>
<td>56</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>3 weeks</td>
<td>81</td>
<td>62</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>4 weeks</td>
<td>84</td>
<td>68</td>
<td>81</td>
</tr>
</tbody>
</table>
SUMMARY

Review of the early literature as well as more recent results show that sulphonamides possess a distinct antimalarial activity. However, when give alone, their action is less marked and slower than that of the antimalarials commonly used in the treatment of the acute attack. Combinations with pyrimethamine provide better results, even in cases of pyrimethamine and chloroquine resistance. This warrants further investigations in an attempt to develop a therapeutic agent suitable for the treatment of such resistant cases. It may also be possible with an appropriate combination of pyrimethamine with a sulphonamide to achieve a satisfactory method for suppressive treatment both in areas with and without pyrimethamine resistance. Three main points must still be carefully studied: 1) the risk of developing malaria resistance against one or both of the components of the combination. 2) The risk of developing bacterial resistance to sulphonamides if these substances are used on a large scale in too low doses. It seems indeed that antimalarial effect with the combination of sulphonamides + pyrimethamine can be obtained with doses of sulphonamides which are below those usually employed in bacterial diseases. Since the range of the ratios providing potentiation is rather large, only ratios of the combination sulphonamides: pyrimethamine should be chosen in which an antibacterial sulphonamidemia is guaranteed. 3) It goes without saying that, although both pyrimethamine and modern sulphonamides, when given by themselves, have proved to possess a large margin of safety, long term administration of their combination should be carefully studied from the point of view of possible side effects.

Substantial evidence has already been produced to show that the long acting sulphonamide Fanasil (Ro 4-4393) given once or once weekly possesses marked schizonticidal activity against \( P. falciparum \). Although its action is slower than that of 4-aminoquinolines, it may be useful as a second choice drug in semi-immune subjects for the therapy of falciparum malaria. Preliminary results show that, when combined with pyrimethamine, Fanasil is highly effective in suppressing fever and asexual parasitemia due to \( P. falciparum \). Single doses of 1 g Fanasil together with 50 mg pyrimethamine seem to be adequate for the treatment of acute falciparum malaria in semi-immune patients. The onset of action of the combination is much more rapid than that of the single components. Weekly doses of 500 mg Fanasil and 25 mg pyrimethamine appear to provide satisfactory suppressive effects against \( P. falciparum \) at least in East Africa. This combination is active on strains which do not respond satisfactorily to the standard doses of pyrimethamine and/or chloroquine and seems to have a satisfactory sporontocidal effect.

Preliminary results indicate that Fanasil alone cannot be recommended for use against the other human malaria parasites. The combination with pyrimethamine appears to be much more effective. East African strains of \( P. falciparum \) seem to respond better to the combination than do Malayan strains of \( P. vivax \) but further trials are required before definite assessment can be made. Fanasil by itself has no gametocytocidal or sporontocidal action but seems to potentiate the effect of pyrimethamine at least on sporogony of \( P. falciparum \).

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