INTRODUCTION

Antibiotics are among the drugs most prescribed by physicians in medical practice. It is also true, however, that increasing bacterial resistance to many of these drugs has been observed in recent years, a phenomenon that appears ascribable to extensive use, misuse, and overuse of antibiotics (1-5). Therefore, it is important that physicians in countries where antibiotic use is regulated become more cautious about issuing prescriptions; and it is important that countries where antibiotics are sold over the counter consider countermeasures capable of correcting obvious abuses—especially since lack of effective regulation (6) can encourage distribution of obsolete, marginally appropriate, or inappropriate drug combinations.

The study reported here reviewed the sources of 77 different fixed combinations of antimicrobial drugs registered for marketing in Central America and listed in the manufacturer's book, Diccionario de especialidades farmacéuticas (5). It also sought to compare the information provided about these combinations (especially indications, contraindications, and side-effects) in the manufacturer's book for Central America as compared to that contained in the Physician's Desk Reference (6) employed in the United States.

SURVEY DATA

All 77 of these formulations consisted of one or more antibiotics combined in some cases with additional medications including enzymes (trypsin, streptokinase, chymotrypsin), analgesics, antihistamines, vitamins, and others. No preparations intended for otic, ophthalmic, or dermal application were included in the survey. At the time of the survey (1984), the antibiotic combinations studied were being marketed in Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama, and the Dominican Republic.

Forty-three (56%) of these combinations were made by European laboratories, 27 (35%) were made by Latin American laboratories, and seven
(9%) were made by U.S. laboratories. The distribution of those manufactured by European and Latin American laboratories within the seven countries covered in this survey is shown in Table 1.

Despite a wide range of different drug dosages and forms involved, most of the 77 combinations studied were registered for use in Central America. Regarding those manufactured by Latin American laboratories, the largest numbers were found to be registered for marketing in Guatemala, Nicaragua, and El Salvador, while somewhat smaller numbers were so registered in Costa Rica, Honduras, the Dominican Republic, and Panama. Also, the highest percentages of these antibiotic combinations were being manufactured in Costa Rica, Guatemala, Mexico, and El Salvador. However, most of the laboratories involved were owned by multinational corporations based in the United States, only a few having local owners.

Regarding the antibiotic combinations manufactured in Europe, many of these laboratories offered a fixed combination of penicillin and streptomycin, despite reports indicating that such combinations have no therapeutic advantage (7). None of these European laboratories is mentioned in the Physicians’ Desk Reference employed in the United States. Indeed, only one of the 77 drug combinations studied was listed in the Physicians’ Desk Reference, this being a Bristol Laboratories product referred to as Azotrex® in the Physicians’ Desk Reference and Uropol by the Diccionario de especialidades farmacéuticas.

**TABLE 1. Distribution to five Central American countries, Panama, and the Dominican Republic of the antibiotic drug combinations studied that were manufactured by European laboratories (43 products) and Latin American laboratories (27 products).**

<table>
<thead>
<tr>
<th>Producing laboratories</th>
<th>Drug products</th>
<th>Costa Rica</th>
<th>El Salvador</th>
<th>Guatemala</th>
<th>Honduras</th>
<th>Nicaragua</th>
<th>Panama</th>
<th>Dominican Republic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Spain</td>
<td>25 (57)</td>
<td>12</td>
<td>20</td>
<td>18</td>
<td>14</td>
<td>19</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Germany</td>
<td>6 (14)</td>
<td>6</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Switzerland</td>
<td>6 (14)</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Austria</td>
<td>2 (5)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Denmark</td>
<td>2 (5)</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Italy</td>
<td>2 (5)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Portugal</td>
<td>1 (2)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>44 (100)</strong></td>
<td><strong>25</strong></td>
<td><strong>36</strong></td>
<td><strong>33</strong></td>
<td><strong>31</strong></td>
<td><strong>37</strong></td>
<td><strong>21</strong></td>
<td><strong>35</strong></td>
</tr>
<tr>
<td>Costa Rica</td>
<td>8 (30)</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Guatemala</td>
<td>6 (22)</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Mexico</td>
<td>6 (22)</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>El Salvador</td>
<td>5 (19)</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Honduras</td>
<td>1 (4)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Panama</td>
<td>1 (4)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>27 (100)</strong></td>
<td><strong>22</strong></td>
<td><strong>25</strong></td>
<td><strong>26</strong></td>
<td><strong>22</strong></td>
<td><strong>26</strong></td>
<td><strong>19</strong></td>
<td><strong>19</strong></td>
</tr>
</tbody>
</table>
In this case the information contained in the latter publication, as compared to the former, is very sketchy. Specifically, portions of the Physicians’ Desk Reference text are as follows:

“Description:

“Each capsule contains T tetrex® (tetracycline phosphate complex) equivalent to tetracycline HCl activity . . . 125 mg
Sulfamethizole . . . . . . . . . . . . . . 250 mg
Phenazopyridine HCl . . . . . . . . . . 50 mg

“Indications:

“Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

“Lacking substantial evidence of effectiveness for the labeled indications.

“Final classification for the less-than-effective indications requires further investigation. . .

“It may be used in mixed infections where the invading organisms are more sensitive to the combination than to either antibacterial agent alone and is not intended for the treatment of infections where complete response to either component might be expected.

“It is indicated in the treatment of cystitis, urethritis, pyelonephritis, ureteritis, and prostatitis due to bacterial infection, prior to and following genitourinary surgery and instrumentation, prophylactically in patients with urethrostomies and cord bladders.

“In geriatrics this drug is particularly useful when exacerbations of infection occur in such conditions as cystocele, prostatitis, and nonspecific urethritis.

“Infections caused by beta-hemolytic streptococci should be treated for at least 10 days to help prevent the occurrence of rheumatic fever or acute glomerulonephritis.

“Contraindications:

“The drug should not be used in patients with a history of sensitivity to one of the components; or in prematures, neonates, pregnant females at term; or in patients with chronic glomerulonephritis, uremia, severe hepatitis, hepatic or renal failure, or severe pyelitis of pregnancy.

“Warnings:

“Certain hypersensitive individuals may develop a photodynamic reaction precipitated by direct exposure to natural or artificial sunlight. . .

Comparable portions of the Diccionario de especialidades farmacéuticas, quoted in part, provide the following information about Uropol:

“Indications:

“Cystitis, urethritis, pyelonephritis, pyelitis, and prostatitis due to bacterial infection. . .

“Contraindications:

“The drug should not be used in chronic glomerulonephritis, uremia, severe hepatitis, hepatic or renal failure, or severe pyelitis of pregnancy.”

The information provided by the Diccionario did not include the “lacking substantial evidence of effectiveness for the labeled indications” cited in the Physicians’ Desk Reference. Also, the latter publication briefly describes the properties of each compound included in the formulation while the Diccionario does not. And finally, unlike the Diccionario, the Physicians’ Desk Reference gives information about the risk of side-effects this antibiotic combination might produce. Clearly, such information needs to be included in the Diccionario, both to guide physicians and to provide a sound basis for marketing and regulating antibiotics in Central America.

It is also true that most of the pharmaceutical laboratories established in Latin American countries are branches of U.S. or European drug companies.
However, the fixed combinations of antibiotics that these Latin American branches manufacture are not usually included in the Physicians' Desk Reference. For instance, Upjohn has registered a combination of novobiocin and tetracycline in Central America under the brand name “Albamicin,” and this is accordingly included in the Diccionario de especialidades farmacéuticas. However, Upjohn does not have this formulation listed as one of its products in the Physicians' Desk Reference, where it merely lists products containing one or the other of these drugs. Similarly, Lederle has registered a combination of tetracycline, salicylamide, acetophenetidine, phenylephrine, and chlorpheniramine in Central America under the brand name “Acropon,” and it has registered tetracycline alone under the brand name “Achromycin.” However, while both products are listed in the Diccionario de especialidades farmacéuticas, only Achromycin® is included in the Physicians' Desk Reference.

**Discussion and Conclusions**

The foregoing suggests that most or all of the 77 fixed Central American antibiotic combinations studied are unnecessary or obsolete (8). Our findings also show that the pharmaceutical companies involved are not using proper standards of advertising in all countries. That is, it appears that the companies are only very cautious about advertising in those countries that have specific regulations against the sale of drugs without prescription and against the inclusion of more than one drug in a single prescribed product. In general, they appear to pay little attention to such matters in countries without regulations governing the manufacture, sale, and use of antibiotics.

In this vein, it seems reasonable to ask why multinational pharmaceutical laboratories located in Costa Rica or Guatemala that are branches of U.S. firms are manufacturing fixed combinations of antibiotics that are not included in the American Physicians' Desk Reference. It is a well-known fact that there are no regulations governing sales of antibiotics in Central America, and that one can buy these drugs over the counter with no prescription. The obvious conclusion is that the pharmaceutical laboratories are aware of this state of affairs, and that policies designed to take advantage of it are encouraging misuse of antibiotics in the region.

This is especially worrisome because resistance to antibiotics is mounting, even in countries where these drugs are carefully regulated; because resistant bacteria have shown a marked ability to travel within and between countries, and because misuse of antibiotics or use of unnecessary or obsolete combinations of them cannot help but aggravate the resistance problem. For these reasons, in addition to the desire to ensure the welfare of individual patients, it would seem important for each Ministry of Health in Central America to consider the role it plays in dispensing antibiotics without prescription and to consider possible ways of modifying that role.

Along these lines it is worth noting that every two years the World Health Organization publishes a report listing those drugs considered essential for Third World countries (9). The report
The results of this survey indicated that only one of the 77 combinations was listed in the Physicians’ Desk Reference; that the information contained in the Diccionario de especialidades farmacéuticas by itself tended to be less than satisfactory; that most of the combinations were manufactured by European pharmaceutical companies or by Latin American branches of U.S. or European firms; that all or nearly all of the 77 drug products were unnecessary or obsolete; and that the prevailing unregulated use of these drug combinations cannot but promote bacterial resistance to a wide range of worthwhile drugs. The authors therefore suggest that manufacturers be required to place in the Diccionario all information about each of their antibiotics that is contained in the Physicians’ Desk Reference. They also recommend that the health authorities involved devise regulations to improve manufacturing standards and regulate access to these drugs, measures that could yield great benefits for health care in Central America as a whole.

REFERENCES


After eight years of steady decline (in 1971-1978), the number of reported cases of congenital syphilis among infants under one year of age in the United States rose in the period 1978-1985 from 108 to 268 per annum. The incidence of congenital syphilis generally reflects the incidence of primary and secondary syphilis among women of childbearing age, as well as the diagnosis and treatment of syphilis in prenatal care programs. In 1985, congenital syphilis rates were highest in areas with high incidences of primary and secondary syphilis. Between 1978 and 1983, primary and secondary syphilis rates for women also increased—to a peak of 7.6 cases per 100,000 women in 1983.

Surveillance data available for the 1983-1985 period indicate that the demographic characteristics of mothers of infants with congenital syphilis did not change appreciably in this period. The mean age for a mother at the time of birth of the infected infant was 24 years (range, 14-43 years); and 133 (30%) of the mothers were under 20 years of age.

In the general population, 95% of all pregnant women have at least one prenatal medical visit; in contrast, only 52% of the mothers of infants with congenital syphilis in 1983-1985 reported having at least one prenatal visit. Among those mothers receiving prenatal care, the mean gestational age at which they were first seen for prenatal care was 22 weeks—late in the second trimester. Preventable failure to diagnose or treat infected mothers who did receive prenatal care contributed to the occurrence of the disease. Among women who received prenatal care, congenital syphilis cases were attributed to failure to screen for syphilis in 18 women (8%); failure to treat 32 pregnant women (14%) with a reactive serologic test for syphilis; and failure to screen 58 women (25%) in the third trimester of pregnancy who lived in an area with a high prevalence of congenital syphilis.