Objective: To determine whether medication use is associated with the development of a pemphigus variant.


Setting: Health maintenance organization in Israel.

Methods: All incident pemphigus variant cases diagnosed from January 1, 1997, through December 31, 2001, among 1.5 million members were identified. A cohort of 150,000 was randomly selected from the health maintenance organization population as the control group. Data on case patients and control subjects, including all medication purchased during the 6 months before the diagnosis, were obtained using the health maintenance organization’s central database.

Results: We identified a total of 363 case patients diagnosed as having pemphigus during the 5-year study (6,961,853 person-years of follow-up). The mean age at diagnosis was 49.8 (SD, 22.7) years, and 53% of the cases were women. Results of a multivariate analysis showed that increased risk for pemphigus was associated with purchasing penicillin during the 6 months before the diagnosis (odds ratio, 2.03; 95% confidence interval, 1.56-2.64). Compared with individuals with no penicillin purchases, we calculated increased risks of 1.84 (95% CI, 1.36-2.49) and 3.02 (95% CI, 1.41-6.49) in those with 1 and 3 or more purchases, respectively. None of the other examined medications, including cephalosporins, angiotensin-converting enzyme inhibitors, dipyrone, anticonvulsants, and nonsteroidal anti-inflammatory drugs, showed similar risks.

Conclusions: To our knowledge, the present research is one of the largest published epidemiological studies on pemphigus variant. The use of computerized medical and administrative databases allowed the detection of case patients in the community, resulting in a higher calculated incidence rate than previously reported. The findings suggest a relationship between the use of penicillin and pemphigus variant. Further studies to assess the nature of this statistical association are warranted.

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Pemphigus is an autoimmune bullous skin disease. The most common variant is pemphigus vulgaris. Epidemiological studies from Israel and the United States suggest that Ashkenazi Jews have an increased risk for pemphigus, with annual incidence rates of 20 per 1 million to 30 per 1 million, compared with other investigated populations such as those of Saudi Arabia (2 per 1 million) and Bulgaria (5 per 1 million).

The etiology, although considered autoimmune because of the presence of pathogenic antibodies directed against desmogleins 3 and 1, may be modified by or the result of endogenous and exogenous factors. The former range from stress to malignancy. The latter include certain food items and exposure to sunlight. Infections and medications may be important extrinsic factors. Viral causes, such as herpes simplex viruses, Epstein-Barr virus, and cytomegalovirus, and bacteria have all been implicated.

Previous studies suggested that a number of different medications can induce pemphigus variants. These can be categorized into the following 3 main groups: (1) drugs containing a sulfhydryl radical, such as penicillamine or captopril (an angiotensin-converting enzyme inhibitor); (2) masked thiols that contain an S molecule and can be converted to a thiol, such as penicillin; and (3) nonthiol or other drugs such as cephalosporins. It has been postulated that, in a case of an abortive form of pemphigus induced by protracted penicillin treatment, the probable trigger was actually penicillamine, which was formed by the metabolic breakdown of the penicillin molecule. In one study, it was estimated that among 168 patients with ar-
thritis who have been given penicillamine for at least 6 months, 8 developed itchy eruptions and 2 had active pemphigus with serious complications.

Except for penicillamine, these drugs induce pemphigus very rarely considering their widespread use. Previous studies of the relationship between medications and pemphigus variant have been based on relatively small numbers of patients and therefore had a low study power. Our study uses a central database that details all medication purchased by an entire insured population. The objective of the present study was to assess the relationship between exposure to certain medications and the development of pemphigus variants.

METHODS

The study was based on data from January 1, 1997, through December 31, 2001, in the Maccabi Healthcare Services (MHS) health maintenance organization (a population of 1.5 million, approximately 24% of the total Israeli population). Established in 1941, MHS has become the nation’s second largest health maintenance organization. According to the National Health Act in Israel—1994, MHS may not bar applicants on any grounds, including age or state of health. Thus, all Israeli population sectors are represented in MHS. Since 1997, diagnoses of MHS members are downloaded daily to a central computer. The database is automatically updated with all hospitalizations and outpatient visits. All medications prescribed by the plan’s physicians, including 140 dermatologists, are recorded.

IDENTIFICATION OF CASES AND COHORT

Incident cases of pemphigus variants were identified by computerized record linkage of the entire cohort to the MHS central computerized database; this allowed the calculation of the incidence rate of the disease among MHS members. All patients who were diagnosed as having pemphigus variants according to the International Classification of Diseases, Ninth Revision, Clinical Modification (codes 694.4 or 964.61) from 1997 through 2001 were identified. The cohort was retrospectively constructed by a random sampling of 10% of the entire MHS population, excluding those with a known pemphigus variant. For every participant, the following data were obtained: age, age at diagnosis, sex, region of residence, and year of immigration to Israel. We also examined the relationship with diabetes and ischemic heart disease using physician diagnosis supported by medication purchase and laboratory tests.

EXPOSURE DATA

We examined all purchases of medications that were previously associated with pemphigus14,16,19,20 during the 6 months before the date that the pemphigus was first diagnosed. These medications included penicillins, cephalosporins, angiotensin-converting enzyme inhibitors, dipyrone, phenobarbiturate, topical anti-inflammatory drugs, and nonsteroidal anti-inflammatory medications. For the cohort participants, data on medication use were obtained for the 6 months from January 1 through June 30, 2000.

STATISTICAL ANALYSIS

For the present analysis, we used the population-based case-cohort study design. Categorical variables (age group, sex, and chronic disease) were compared with those of the standard population. We used the Pearson χ² test of significance, with P values of less than .05 considered significant and correction for continuity where appropriate. Odds ratios (ORs) and 95% confidence intervals (CIs) of pemphigus were derived from stepwise unconditional multiple logistic regression models, fitted by the method of maximum likelihood. In the multivariate logistic regression, the following predictors in addition to medication use were assessed: age at diagnosis, sex, region of residence (southern, northern, or central Israel), and the presence of chronic diabetes and cardiovascular disease (including congestive heart failure and ischemic heart disease) as binary variables.

RESULTS

GENERAL FINDINGS

During the observation period from 1997 through 2001 (6,961,853 person-years of follow-up), a total of 363 incident cases of pemphigus were identified, representing an incidence rate of 5.3 per 100,000 person-years. The mean (SD) age at diagnosis was 49.8 (22.7) years, and 52.9% were women. The age-specific rates (and Fisher 95% CI) of pemphigus in the MHS population are shown by sex in the Figure. Individuals younger than 35 years had the lowest rate (<5 per 100,000); at 45 years of age, the rate increased sharply with increasing age in both sexes, reaching 30 per 100,000 among individuals 75 years or older. Pemphigus variants do not seem to be associated with the presence of comorbid diabetes; however, there was a significant association with cardiovascular disease (Table 1).

CASE-COHORT STUDY

A total of 149,423 members of the MHS health maintenance organization were randomly selected as cohort control subjects to the 363 identified cases. The demographic characteristics of the case patients with pemphigus differed significantly from those of the controls with respect to subject age, as shown in Table 1. More than one fifth of the case patients had made at least 1 purchase of penicillin during the 6 months before diagnosis; this is compared with 13.5% of the controls. After adjusting for age and sex, the OR associated with penicillin purchase...
was 1.97 (95% CI, 1.52-2.57). This was the only significant difference found in medication purchases between cases and controls after adjusting for age and sex (Table 2). In the multivariate model, age was significantly associated with increased risk (for every year of age, OR, 1.04; 95% CI, 1.03-1.05) for pemphigus. Individuals with diabetes mellitus had a significantly reduced risk (OR, 0.27; 95% CI, 0.14-0.51). Use of penicillin remained significant with an OR of 2.03 (95% CI, 1.56-2.64), as shown in Table 2.

A significant (P < .001) trend of increased risk was found between the number of penicillin packs purchased and the risk of pemphigus. The fully adjusted OR of the individuals who purchased 3 or more packs was 3.02 (95% CI, 1.41-6.49) compared with nonusers, as shown in Table 3.

### Table 1. Distribution of Demographic Characteristics and Chronic Diseases Among Pemphigus Cases and Cohort Controls of the MHS HMO

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n = 363)</th>
<th>Cohort Controls (n = 149,423)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>171 (47.1)</td>
<td>77,041 (51.6)</td>
<td>.10</td>
</tr>
<tr>
<td>Female</td>
<td>192 (52.9)</td>
<td>72,382 (48.4)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>90 (24.8)</td>
<td>78,271 (52.4)</td>
<td></td>
</tr>
<tr>
<td>35-44</td>
<td>59 (16.3)</td>
<td>27,253 (18.2)</td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>54 (14.9)</td>
<td>20,734 (13.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>55-64</td>
<td>50 (13.8)</td>
<td>11,023 (7.4)</td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>63 (17.4)</td>
<td>70,60 (4.7)</td>
<td></td>
</tr>
<tr>
<td>≥75</td>
<td>47 (12.9)</td>
<td>50,82 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Region of residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North</td>
<td>75 (20.7)</td>
<td>28,690 (19.2)</td>
<td>.70</td>
</tr>
<tr>
<td>Center</td>
<td>250 (68.9)</td>
<td>105,859 (70.8)</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>38 (10.0)</td>
<td>14,874 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Chronic diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>29 (8.0)</td>
<td>4908 (3.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10 (2.8)</td>
<td>5896 (3.9)</td>
<td>.34</td>
</tr>
</tbody>
</table>

Abbreviations: HMO, health maintenance organization; MHS, Maccabi Healthcare Services.
*Calculated by means of the Pearson χ² test.

### Table 2. Purchase of Selected Medications Among Case Patients With Pemphigus During the 6 Months Before Diagnosis and Among Cohort Controls During the First 6 Months in 2000

<table>
<thead>
<tr>
<th>Medication</th>
<th>No. (%) of Subjects</th>
<th>OR (95% CI)</th>
<th>Initial Comparison†</th>
<th>Adjustment 1‡</th>
<th>Adjustment 2§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporin</td>
<td>28 (7.7)</td>
<td>1.00 (0.92-1.09)</td>
<td>0.12</td>
<td>1.21 (0.96-1.52)</td>
<td>1.20 (0.94-1.54)</td>
</tr>
<tr>
<td>Penicillin</td>
<td>76 (20.9)</td>
<td>1.00 (0.92-1.09)</td>
<td>0.01</td>
<td>1.54 (1.20-2.00)</td>
<td>1.83 (1.41-2.38)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>25 (6.9)</td>
<td>1.00 (0.92-1.09)</td>
<td>&lt;.001</td>
<td>1.17 (1.08-1.67)</td>
<td>1.30 (1.07-1.59)</td>
</tr>
<tr>
<td>Dipyrone</td>
<td>20 (5.5)</td>
<td>1.00 (0.92-1.09)</td>
<td>&lt;.001</td>
<td>1.14 (1.01-1.30)</td>
<td>1.25 (1.11-1.63)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>39 (10.7)</td>
<td>1.00 (0.92-1.09)</td>
<td>&lt;.001</td>
<td>2.24 (1.85-2.72)</td>
<td>0.90 (0.63-1.28)</td>
</tr>
<tr>
<td>Topical anti-inflammatory drugs</td>
<td>26 (7.2)</td>
<td>1.00 (0.92-1.09)</td>
<td>&lt;.001</td>
<td>1.67 (1.48-2.00)</td>
<td>1.16 (0.96-1.38)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio.
*Calculated by means of the Pearson χ² test.
†Compared with no purchases.
‡Adjusted for age and sex.
§Adjusted for age, sex, region, diabetes mellitus, and cardiovascular disease.

### Table 3. Number of Penicillin Packs Purchased During the 6 Months Before Diagnosis With Respective ORs

<table>
<thead>
<tr>
<th>No. of Penicillin Packs*</th>
<th>No. of Subjects</th>
<th>OR (95% CI)</th>
<th>Initial Comparison†</th>
<th>Adjustment 1‡</th>
<th>Adjustment 2§</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>287</td>
<td>1.00 (0.92-1.09)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>1</td>
<td>53</td>
<td>1.00 (0.92-1.09)</td>
<td>1.57 (1.17-2.11)</td>
<td>1.83 (1.36-2.46)</td>
<td>1.84 (1.36-2.49)</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>1.00 (0.92-1.09)</td>
<td>2.00 (1.20-3.30)</td>
<td>2.57 (1.55-4.27)</td>
<td>2.54 (1.52-4.26)</td>
</tr>
<tr>
<td>≥3</td>
<td>7</td>
<td>1.00 (0.92-1.09)</td>
<td>2.15 (1.01-4.56)</td>
<td>3.00 (1.41-6.37)</td>
<td>3.02 (1.41-6.49)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.
*P < .001 for trend.
†Compared with no purchases.
‡Adjusted for age and sex.
§Adjusted for age, sex, region, diabetes mellitus, cardiovascular disease, cephalosporin, angiotensin-converting enzyme inhibitors, dipyrone, anticonvulsants, nonsteroidal anti-inflammatory drugs, and topical anti-inflammatory drugs.

This study shows that, among the examined medications, only penicillin is associated with the development of pemphigus. The increased ORs seen with increasing exposure support this observation. Previous retrospective surveys on pemphigus have been limited to a single geographic region or hospital ward. The strengths of this study are its population-based design, the inclusion of case...
patients diagnosed and treated in the community, and the use of complete data capture of prescribed medications and diagnosis. This eliminates threats of recall, selection, and surveillance bias, which are important methodological limitations of previous case reports. The comprehensive data sources used to identify cases in this study may explain the relatively high annual incidence rate calculated in our study (5 per 100,000) compared with 2 per 100,000 to 3 per 100,000 in a previous study\(^\text{4}\) that used data from the 1960s and 1970s. This difference can also be explained by the development of better diagnosis methods and increased awareness of the disease.

However, this research has a number of important limitations. These limitations are related to the problems of conducting epidemiological research on databases that have been designed for administrative and medical purposes\(^\text{22}\) and those inherent to case-cohort studies. Case-cohort studies determine the relative importance of a predictor variable in relation to the presence or absence of the disease. This type of study is therefore useful for generating hypotheses that can then be tested using other types of study. It should be remembered that confounding factors are a major limitation of case-cohort studies.\(^\text{23}\) Within the group of identified case patients with pemphigus, there may be misdiagnosed cases that we were not able to identify. The scope of this study did not allow us to validate each case with the pathological findings of the biopsy, and thus all pemphigus variants are examined together in this study. It could be that the index case patients were diagnosed—or misdiagnosed—as having a sore throat and then treated with penicillins or cephalosporins, when they actually had a few intraoral erosions of pemphigus variant before it was finally diagnosed.

It cannot be determined from this study whether penicillin use is causally related to pemphigus variant or whether the indication for use, overall weakened immune function, or other factors are pertinent underlying exposures. Penicillin is administered for infection, which itself is an important pemphigus trigger.

The findings of previous research that other medications such as cephalosporins or captopril may trigger pemphigus are not supported by this study. The present study may have been underpowered to show this effect, but information about induction of pemphigus by cephalosporins or angiotensin-converting enzyme inhibitors is important in future research.

Similar to a previous report from Israel,\(^\text{21}\) women in our study constituted a little more than 50% of the entire subject population. In the Mediterranean regions, pemphigus vulgaris, which accounts for more than 80% of all pemphigus cases,\(^\text{23}\) is known to affect more women than men in a ratio of approximately 1:1.5.\(^\text{24-27}\) In this aspect, Israel is similar to northern countries, where the incidence of the disease is equal between the sexes. This may be partly owing to the large population of new immigrants to Israel from the former Union of Soviet Socialist Republics.

This study suggests that that there is an association between penicillin exposure and the diagnosis of pemphigus variants. Further study is warranted to determine whether penicillin is causative in the development of the disease or is a reflection of other confounding effects.

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Correspondence: Anthony D. Heymann, BSc MB, MS, MRCGP, MHA, Maccabi Healthcare Services, 27 HaMered St, Tel Aviv 68125, Israel (Heymann_md@mac.org.il).

Author Contributions: Study concept and design: Heymann and Green. Acquisition of data: Heymann, Kramer, and Shalev. Analysis and interpretation of data: Heymann, Chodick, and Shalev. Drafting of the manuscript: Heymann. Critical revision of the manuscript for important intellectual content: Heymann, Kramer, Green, and Shalev. Statistical analysis: Chodick. Administrative, technical, and material support: Kramer and Shalev. Study supervision: Heymann and Green.

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