antecedent skin disease and precedes the classical ductal vesication. It is possible that the 5 cases in this series which followed cement or other eczemas may belong to this group.

Oedema of the Sweat Duct
Previous work has shown that the earliest lesion in miliaria rubra is a hydropic change in the basal layer of the sweat duct. Identical changes can be produced by compresses of hypertonic saline and by iontophoresis of salt solutions. Further work has shown that the chronic miliaria subject excretes a higher concentration and a larger quantity of salt through both sweat glands and kidneys. There is no reason to believe that this phenomenon results from a higher intake of salt and both this and other more recent experiments suggest that a disturbed adrenal cortical function may be an important factor. The significance of these findings and tentative suggestions may be supported by the known relationship between acclimatization, adrenal cortical function and salt metabolism. Sargent and Slutsky and Ladell have touched on aspects of this problem: the possibility of dysacclimatization, adrenal cortical function and salt metabolism. It is probable that high concentrations of sodium chloride are the only factor in the production of miliaria. Several of our control subjects without miliaria also had high concentrations under experimental conditions though never to the extent of the sweat becoming hypertonic as compared with blood plasma, as seen in some miliaria cases. Furthermore, it is far easier to produce artificial miliaria with hypertonic salt compresses in previous sufferers from miliaria, as was also found by Shelley and Horvath with iontophoresis. Other sweat constituents may play an essential part; urea, which is known to facilitate the entry of sodium into cells, produces an alteration in the cellular sodium-potassium ratio consequent on the breakdown of glycogen, and even allergens may have to be considered.

The hypothesis presented here is that prolonged stress, whether from heat, trauma, illness, alcoholism or psychic stimuli, may lead to adrenal dysfunction; this manifests itself by an increased concentration of salt in the sweat and this, in its turn, provides one of the essential local prerequisites for the development of miliaria. If Ladell's tentative suggestion is proved correct, then the miliaria itself would act as an additional stress leading to Selye's 'exhaustion stage'. The hypothesis is sketched diagrammatically in Fig. 1, where a possible vicious circle is seen.

Referring to Table II we see that forms of stress such as a change to hotter working conditions (23 cases), trauma in 3 and 'other stress' in 4 subjects occurred in 60% of these cases; we cannot say how many more are exposed to emotional stress (including fear) or bouts of alcoholic excess, but we suspect that these, too, account for an appreciable number.

It has not been suggested that high concentrations of sodium chloride are the only factor in the production of miliaria. Several of our control subjects without miliaria also had high concentrations under experimental conditions though never to the extent of the sweat becoming hypertonic as compared with blood plasma, as seen in some miliaria cases. Furthermore, it is far easier to produce artificial miliaria with hypertonic salt compresses in previous sufferers from miliaria, as was also found by Shelley and Horvath with iontophoresis. Other sweat constituents may play an essential part; urea, which is known to facilitate the entry of sodium into cells, produces an alteration in the cellular sodium-potassium ratio consequent on the breakdown of glycogen, and even allergens may have to be considered.

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REFERENCES

PRENYLAMINE ('SEGONTIN') IN PROPHYLAXIS OF ANGINA PECTORIS ATTACKS
D. P. STABLES, M.B., B.Chir. (Camb.), Registrar, C. M. PROWSE, *M.B., B.Ch., F.Ch.P. (S.A.), formerly Registrar, AND G. A. ELLIOTT, M.D., F.R.C.P., Professor of Medicine, University of the Witwatersrand, Johannesburg.

Prenylamine lactate is marketed in South Africa under the name of segontin as a specific coronary vasodilator for use in the prophylaxis of angina pectoris. Chemically it is N-(3:3 diphenyl propyl) -1 methyl-2-phenyl ethylamine lactate. The drug has been held to increase coronary blood flow in experimental animals, although many of the studies were based on measurements of coronary sinus blood flow. The assumption that coronary sinus drainage is a fixed percentage of total and left-ventricular coronary flow has recently been questioned. The drug has minor sympatholytic, sedative and monoamine oxidase-inhibitory effects.
Favourable reports on the clinical application of prenylamine appeared first in the German literature. The observations did not appear to be adequately controlled. Numerous drugs have in fact been introduced for the prophylaxis of anginal attacks, but none to date have been proved to have more than a placebo effect in carefully controlled trials. The fallacy of clinical impressions was stressed as long ago as 1933 by Evans and Hoyle, who found that 38% of patients receiving a placebo reported improvement in their angina. The importance of including objective methods of assessment has been emphasized by Mitchell.

Of the 4 controlled trials on prenylamine published before the beginning of the present study, 3 reported results favourable to the drug. Overkamp alternated drug and placebo by the day, but the manufacturers claim that the drug is slowly excreted and that its effects last up to a week after treatment is withdrawn. The numbers of patients completing the trials reported by Baumgarten and Kerridge et al. were small, respectively 9 and 10, and it is noteworthy that in neither did the objective tests of exercise tolerance confirm the subjective improvement claimed. Böhm et al. described a study in which prenylamine was compared with 2 unidentified commercially available drugs with reputed anti-anginal action. The paper states that the results of the trial showed no clear differences between the different substances, but surprisingly this negative finding does not receive any comment in the authors' discussion.

Method

Thirty-four outpatients with a history of angina pectoris were studied. The group consisted of 15 men and 18 women, their ages ranging from 45 to 70. In all cases the angina had been unchanged in frequency over the previous 6 months and no episode of myocardial infarction had occurred in the past year. One patient had in addition a mild mitral stenosis and 1 suffered from essential hypertension well controlled on a diuretic and reserpine, the dosages of which were unchanged in frequency.

A standard double-blind technique with crossover was utilized. All patients received the test drug and an identically dispensed lactose placebo, each for a period of 2 months. The tablets were supplied in identical unlabelled containers. Equal numbers of patients were started at random on prenylamine or placebo by a ward sister, to whom the tablets were known only as A or B. This code was broken only after the preliminary analysis of results at the completion of the trial. At the end of the first 2 months' period each treatment was changed. The patients were not informed of this, but before being given new tablets they were asked to return any unused tablets from the previous issue; it was explained that the latter were 'out of date'.

The dosage employed was 1 tablet 3 times daily of prenylamine (15 mg.) or placebo. All other drugs utilized in the prophylaxis of angina pectoris, including sedatives, were discontinued a week before the beginning of the trial. Free access to glyceryl trinitrate for treatment of attacks was allowed.

Patients attended a special clinic monthly or, in the case of those subjected to exercise tests, at fortnightly intervals. Each patient saw 1 physician throughout the trial. At each visit subjective impressions of the effect of the tablets were noted, and the pulse rate, blood pressure and ECG were recorded and an inquiry made after possible side-effects. The patients were asked to record their consumption of glyceryl trinitrate tablets and to present the list for checking at each visit. At the end of the study the patients were informed that they had received 2 different medications and were asked to state a preference on the basis of their subjective impressions during each 2-month period.

A series of exercise-tolerance tests was performed at the beginning of the study and at fortnightly intervals. Thirteen patients were selected, mainly on their ability to distinguish between pain and dyspnoea as the factor limiting exertion. The subject stepped up and down a sturdy platform 20 cm. high, in time to a metronome at a rate of 63 steps per minute. Exercise was stopped with the development of chest pain and the time recorded on a stopwatch. The patients were not told the results of their performance. The test was always done between 2-3.15 p.m. with the exception of 1 patient who attended between 10-11 a.m., and all bore a reasonably constant relationship to meals. A comfortably warm, centrally heated room was used. Comparable clothing was worn on each occasion and the patient was allowed to rest for 15 minutes before the test was done, during which time no glyceryl trinitrate tablets were consumed.

Results

Four patients failed to complete the trial. One was admitted to hospital with a myocardial infarction and another developed an intercurrent illness, both while taking the placebo. Two stopped attending because they felt the tablets (which were prenylamine) to be inferior to their previous therapy. Of interest is that previous treatment considered by 1 patient to be superior to our course of prenylamine was in fact a course of prenylamine prescribed by a general practitioner. As these exclusions occurred with equal frequency on both treatments, they cannot disturb the final comparisons.

The results for the 30 patients completing the trial are set out in Table I. No significant difference in patient preference, glyceryl trinitrate consumption or exercise tolerance could be demonstrated. The drug was without effect on pulse or blood pressure and no consistent change in the ECG accompanied its administration. There were no side-effects attributed to the drug. Two patients complained of slight drowsiness while they were receiving the placebo.

Twenty-four of the patients completing the trial considered 1, or more often both, courses of tablets to be better than their previous therapy. Five were unchanged and 1 felt worse.

**TABLE I. RESULTS IN 30 PATIENTS**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Prenylamine</th>
<th>Placebo</th>
<th>Nil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall preference as expressed by patient</td>
<td>8</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Glycerol trinitrate consumption per patient mean time period</td>
<td>30-3</td>
<td>27-33</td>
<td>p &gt; 0.05</td>
</tr>
<tr>
<td>range</td>
<td>0-202</td>
<td>0-209</td>
<td></td>
</tr>
<tr>
<td>Exercise tolerance in seconds</td>
<td>mean</td>
<td>146-7</td>
<td>170-3</td>
</tr>
<tr>
<td>(13 patients)</td>
<td>range</td>
<td>58-352</td>
<td>54-478</td>
</tr>
<tr>
<td>Average of 3 or more often 4 tests in each period</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DISCUSSION**

It is concluded that prenylamine is of no greater value than a placebo in the prevention of anginal attacks in the dosage of 45 mg. daily, recommended by the manufacturers as suitable for maintenance therapy in the majority of cases. While the present investigation was in progress, 3 trials utilizing a dose of 90 mg. daily were reported. Two found this dosage to be ineffective. The third was cautiously favourable. However, the latter may be criticized for employing patient preference as the single indicator of benefit. The other 2 measured the number of anginal attacks or the consumption of glyceryl trinitrate. None employed an exercise-tolerance test.

The negative results on assessment of all 3 criteria of success within the present controlled trial, namely patient preference, glyceryl trinitrate consumption and exercise tolerance, contrast sharply with the beneficial effects
claimed by a majority of the patients, when asked to compare the trial as a whole with their previous therapy. Even when allowance is made for those who failed to complete the study, 70% of the original group felt improved and only 14% were worse. These figures are remarkably similar to those obtained from many of the uncontrolled observations on prenylamine, notably the report of Ratschow and Schoop whose finding of a remarkably similar result to rats it will give rise to liver cancers. However, this finding had been examined for the quality and condition of its toxicity to the kidneys. But even more important, the article adds that other recent reports that it had caused liver damage in man as well as in experimental animals.

Prenylamine in the dosage used, was no more effective than the inert tablet. No side-effects could be ascribed to the drug. A remarkable placebo effect was induced by the trial as a whole and the significance of this in relation to uncontrolled observations is discussed.

**REFERENCES**


**CARCINOGENS IN CIGARETTE SMOKE**

**LEWIS S. ROBERTSON, President, National Cancer Association of South Africa**

The National Cancer Association of South Africa is privileged to announce a promising development in the research into the connection between cigarette smoke and lung cancer. A Pretoria scientist, Dr. W. J. Serfontein, and Mr. P. Hurter, a senior student of the Organic Chemistry Department of the Pretoria University, have just discovered that the smoke of a brand of South African cigarette contains a highly active cancer-producing agent, or rather group of agents, known as 'nitrosamines'.

The results obtained by Dr. Serfontein not only provide additional evidence of a possible causal relationship between lung cancer and smoking, but, perhaps more significantly, open up the possibility of selectively removing some of the carcinogenic agents from tobacco smoke. This finding is based on fundamental chemical research work.

Cancer research workers have speculated on the possible occurrence of nitrosamines in tobacco tar and the significance of these compounds as cancer-causing agents, responsible for the increased cancer incidence observed among tobacco smokers. Dr. Serfontein has succeeded in developing a method which he has applied to the analysis of tar obtained from cigarette smoke for its nitrosamine content, and he has proved that this carcinogenic (cancer-producing) substance is present in South African cigarette tobacco smoke. The significance of this discovery lies in the fact that although the nitrosamine compound is known as a carcinogen, this is the first time that it has been established beyond doubt that various nitrosamines occur in cigarette smoke.

Just how potent the nitrosamine compound is, will be gathered from a perusal of an article which appeared in a recent World Health Organization Technical Report (Series No. 276, 1964.)

In this report mention is made that the first of this group of increasingly interesting and important cancer-causing agents was dimethylnitrosamine, which was described to be carcinogenic by research workers Magee and Barnes. The compound had been examined for the quality and condition of its toxicity by following reports that it had caused liver damage in man as an occupational hazard. According to Magee and Barnes the compound is notable in several respects: If fed continuously to rats it will give rise to liver cancers. However, if administered only once, it will cause tumours of both liver and kidneys. But even more important, the article adds that other investigators have found that by injecting diethylnitrosamine under the skin of a hamster it will cause cancer of the bronchi, a kind of cancer which it is notoriously difficult to induce in this experimental animal.

In addition, it is known from the work of Drucke in Germany, that an interesting relationship between the structure of various nitrosamines and the organs affected by them exist in experimental animals. In this respect it may be possible that the present discovery will shed light on another observation, namely that among smokers there is also a tendency for an increase in the incidence of cancers other than the lung. Dr. Serfontein has also adapted his method to the determination of nitrosamines in foodstuffs and is applying the method in air pollution studies.

It is becoming increasingly evident that many smokers will continue smoking despite warnings and, in so doing, will continue to expose themselves to what may be considered one of the most serious health hazards. Dr. Serfontein believes that 'amelioration of the situation can only be achieved by the development of safer tobacco products, an approach which should prove acceptable to all parties concerned'. This discovery has opened up the possibility of the selective removal of certain of the potentially harmful compounds in cigarette smoke.

In conclusion I wish to express my great pleasure that the Cancer Association was able to make a small contribution towards Dr. Serfontein's discovery in that it has contributed towards his travelling and subsistence expenses when he recently proceeded overseas in connection with his studies. An application for a substantial research grant has been submitted by Dr. Serfontein to the National Cancer Association of South Africa. This application along with others will be subject to the scrutiny of the Cancer Association's National Research Committee which consists of leading scientists specializing in many fields. I do not wish to prejudice the issue in any way, but it seems possible that next year will see a closer liaison between Dr. Serfontein and the Cancer Association. This scientist deserves the support of the Association and if the Research Committee agrees, such support will be forthcoming. The Cancer Association and the public of South Africa will see to that.