Allergenicity of Piperazine: A Study in Environmental Aetiology

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This paper reports an apparent biological difference between two otherwise identical preparations of piperazine hexahydrate. It reports the cutaneous irritancy and allergenicity of this substance and records the effect of environmental temperature on those properties, particularly the former. Finally, it reports severe, delayed asthma-like response to piperazine exposure. Interrogation of companies engaged in the manufacture of the substance revealed that the unwelcome effects reported here have quite commonly affected workers in the United States, the United Kingdom, Sweden, South Africa, and elsewhere in Sydney. The only report known to me is that of Foussereau (1963), who mentions cutaneous sensitization of nursing staff. It is remarkable that the chemical companies concerned should not have published reports of these ill effects. One may conclude from this study that in seeking to prevent industrial contact dermatitis consideration of the effective environmental temperature may well prove as rewarding as other more conventional measures.

Piperazine (piperazine hexahydrate has the empirical formula, C₅H₁₂N₂H₂O₆) is used medicinally in the form of the hydrate, the citrate, the tartrate, the phosphate, and the adipate and in various other more complex compounds. It was first used about the turn of the century for the treatment of gout but its relative ineffectiveness led it into desuetude (Brown, Chan, and Hussey, 1956). It has lately been extensively used as a human and animal anthelmintic, and certain of its compounds have been investigated for the treatment of cancer (McNair, Wibin, Hoppe, Schmidt, and de Peyster, 1963; Mikhailov, Dorokhova, and Smolina, 1963), radiation sickness (Foye and Kay, 1962), and angina pectoris (Jouve, Gras, and Benyamine, 1963).

The toxicity of piperazine has been reviewed by White and Standen (1953) who report that 'no important toxic effects have been recorded', and by Brown et al. (1956), who reached the same conclusion. Certain toxic effects are generally recognized, however. Martindale (1958) records that mild diarrhoea, vertigo, muscular incoordination, and paresthesiae may occur rarely and, more rarely still, nausea, vomiting, blurred vision, and urticaria. These are attributed to overdosage or accumulation of the drug.

There is only uncertain evidence that piperazine is allergenic. Hill (1957) has reported the case of a 5-year-old girl who had been given piperazine citrate without ill-effect but who, three months later, developed an acute urticaria after being given only a single further dose. Ureles (1958) has reported a case in which the administration of piperazine was followed by acute urticaria and fever and subsequently by the development of inflammatory arthritis and lymphadenopathy. Shanker and Gulati (1960) have reported a case of purpura following the administration of piperazine. The most recent such report is that of Butler (1968).

On the other hand, Ratner and Flynn (1955) rigorously investigated the anaphylactogenic properties of piperazine citrate in the guinea-pig and concluded that 'this drug has been shown to be non-anaphylactogenic in the lower animal; it should be regarded as a non-allergenic drug.'

More recently, attention has turned to the occasional neuropathogenic effects of piperazine (Point, 1965; Neff, 1966; Nickey, 1966; Schuch, Stephan, and Jacoby, 1966).

Only in the French literature (Foussereau, 1963) has piperazine been reported to cause contact dermatitis; its action as a respiratory allergen is, so far as I am aware, unrecorded. This paper discusses these two aspects of its toxicity, which represent a hazard to those who are occupationally exposed to the substance rather than to those to whom it is therapeutically administered. It is

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shown that the cutaneous response to piperazine is highly dependent on environmental temperature.

The Present Study

The present study was undertaken when it appeared that workers exposed to piperazine were developing allergic reactions to it. The preparation concerned was a sheep drench in the manufacture of which piperazine hexahydrate and tartaric acid were mixed in aqueous solution, converting the piperazine to the tartrate, to which solution copper sulphate and sodium arsenite were added. Every effort was made to protect the exposed men. While handling piperazine they wore gauntlets extending almost to the armpits, a great apron covering them from above the nipple line nearly to the ankles, and a positive-pressure respirator totally enclosing the head and nearly the whole of the thorax. After finishing the job they stripped, showered, and changed to clean clothes. These measures failed to isolate them from the allergen, and, in the course of a year, four of seven exposed operatives at Kingsgrove Laboratories were sensitized.

The main suppliers in Australia, drawing on various sources of supply themselves, have handled piperazine continuously since 1951, when it was first introduced here as an anthelmintic, and they have handled mainly the hexahydrate and the citrate. They have taken no precautions whatever and yet, despite careful supervision, they are unaware of any allergic manifestations attributable to piperazine. The man in charge of the piperazine operation at Kingsgrove Laboratories visited the suppliers and studied their handling methods. He was unable to observe any precaution taken there that was not taken by Kingsgrove Laboratories; indeed at the main suppliers the operatives appeared to take no precautions, they wore no protective clothing, they simply broke the piperazine into convenient lumps and, bare-handed, tossed it into the mixing vat.

It seemed, therefore, advisable at this stage not merely to patch test with the piperazine hexahydrate used by Kingsgrove Laboratories, referred to here as piperazine-K, but at the same time to test also with the piperazine hexahydrate used by the other firm (piperazine-BW), a sample of which was made available.

Cutaneous Irritation

Methods and Materials Piperazine hexahydrate, although a highly alkaline substance, is not generally recognized as an irritant. Initially, two subjects strapped the crystalline substance to their forearms for 48 hours to establish that lay volunteers were not asked to expose themselves to any undue risk. From December 1964 to February 1966, a series of observations was made in which aqueous solutions of 20 and 25 g./100 ml. were prepared and patches soaked in these were applied to the skin for periods of up to 48 hours. Fortunately all solutions used were kept and, when paradoxical results were obtained, were assayed for their piperazine content and were all shown to have been accurately made up.

Results It appears from Table I that piperazine hexahydrate applied for 48 hours in an aqueous solution containing 25 g./100 ml. may act as a primary irritant. The most remarkable finding, however, is that piperazine-K appears to be much more irritant than piperazine-BW, the two preparations being apparently identical and both having been shown to conform to the specifications of the B.P. and the U.S.P. Application of the t test shows that the difference is significant with $p < 0.02$ and $0.01$. However, as the number of subjects was rather small and the result so unexpected, it was advised that the result should be confirmed by a larger sample. The observation was repeated in February 1966, and the results of December 1964 were reproduced (Table II). If one combines the results of December 1964 and of February 1966, the sample is sufficiently large and the difference between the irritant effect of the two piperazines clearly significant. The t test gives a value of $p < 0.01$.

Cutaneous Allergenicity

Methods and Materials Piperazine is not a widely recognized allergen (Schwartz, Tulipan, and Birmingham, 1957) and the concentration that should be used to test for sensitivity was not known. It was thus necessary to determine the concentration below which there would be no irritant effect. This was done concurrently with the investigation of primary irritancy in December 1964.

Eight men in whom there was no clinical evidence of sensitivity wore patches moistened with aqueous solutions containing 25, 5, 1, and 0.1 g./100 ml. piperazine hexahydrate. From this observation it was concluded that piperazine did not operate as a primary irritant at concentrations of 5 g./100 ml. or less.

Four men in whom there was clinical evidence of sensitivity were also tested. Two of these had already been tested elsewhere for sensitivity to piperazine (using irritant concentrations) and had given strongly, indeed incapacitatingly, positive reactions and so the 25 and 5 g./100 ml. solutions were not used on them. Another of the four men had had no positive patch test, but in view of the strongly suggestive clinical history the 25 g./100 ml. solution was omitted.

Results These are shown in Table III. It appears that, for patch testing, a solution of
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TABLE I
RESPONSE OF NON-SENSITIZED MEN TO APPLICATION OF AQUEOUS PATCHES OF TWO PREPARATIONS OF PIPERAZINE HEXAHYDRATE CONTAINING 25 G./100 ML.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Hours Patch Worn</th>
<th>Reaction</th>
<th>Score</th>
<th>Hours Patch Worn</th>
<th>Reaction</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.M.</td>
<td>48</td>
<td>Dark erythema of patch area</td>
<td>2</td>
<td>48</td>
<td>Erythema less than patch area</td>
<td>1</td>
</tr>
<tr>
<td>F.J.</td>
<td>25</td>
<td>Dark erythema greater than patch area</td>
<td>3</td>
<td>25</td>
<td>Dark erythema of patch area</td>
<td>2</td>
</tr>
<tr>
<td>T.R.</td>
<td>48</td>
<td>Erythema greater than patch area</td>
<td>3</td>
<td>48</td>
<td>Nil</td>
<td>0</td>
</tr>
<tr>
<td>C.M.</td>
<td>48</td>
<td>Nil</td>
<td>0</td>
<td>48</td>
<td>Nil</td>
<td>0</td>
</tr>
<tr>
<td>R.N.</td>
<td>48</td>
<td>Erythema and oedema of patch area with vesiculation</td>
<td>4</td>
<td>48</td>
<td>Erythema less than patch area</td>
<td>1</td>
</tr>
<tr>
<td>S.T.</td>
<td>48</td>
<td>Erythema and oedema of patch area</td>
<td>2</td>
<td>48</td>
<td>Nil</td>
<td>0</td>
</tr>
<tr>
<td>N.M.</td>
<td>48</td>
<td>Nil</td>
<td>0</td>
<td>48</td>
<td>Nil</td>
<td>0</td>
</tr>
<tr>
<td>D.W.</td>
<td>48</td>
<td>Marked vesiculation</td>
<td>4</td>
<td>48</td>
<td>Nil</td>
<td>0</td>
</tr>
</tbody>
</table>

Scoring as for Table I.

Effect of Temperature on Cutaneous Response

Although cutaneously sensitized subjects reacted a little more strongly to piperazine-K than to piperazine-BW, the difference is not significant, nor does weighting of score for duration of exposure materially affect this position. Much more important is the fact that all four subjects suffered an exacerbation of their symptoms attributed to piperazine remote from the patch sites.
TABLE III
RESPONSE OF MEN TO AQUEOUS PATCHES OF PIPERAZINE HEXAHYDRATE
PERIOD OF OBSERVATION 8-10 December 1964

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Clinical Evidence of Allergy to Piperazine</th>
<th>Piperazine-K g./100 ml.</th>
<th>Hours</th>
<th>Reaction</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.W.</td>
<td>60</td>
<td>Ecema; nocturnal dyspnoea</td>
<td>1.0</td>
<td>30</td>
<td>Nil locally</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.1</td>
<td>48</td>
<td>Nil locally</td>
<td>0</td>
</tr>
<tr>
<td>J.M.</td>
<td>34</td>
<td>Ecema; doubtful nocturnal dyspnoea</td>
<td>5.0</td>
<td>24</td>
<td>Erythema and vesiculation</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
<td>48</td>
<td>Nil</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.1</td>
<td>48</td>
<td>Nil</td>
<td>0</td>
</tr>
<tr>
<td>K.D.</td>
<td>38</td>
<td>Ecema</td>
<td>25.0</td>
<td>28</td>
<td>Erythema greater than patch area, slight vesiculation</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.0</td>
<td>28</td>
<td>Erythema of patch area</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
<td>48</td>
<td>Nil</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.1</td>
<td>48</td>
<td>Nil</td>
<td>0</td>
</tr>
<tr>
<td>A.N.</td>
<td>60</td>
<td>Ecema</td>
<td>1.0</td>
<td>48</td>
<td>Erythema and vesiculation</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.1</td>
<td>48</td>
<td>Nil</td>
<td>0</td>
</tr>
</tbody>
</table>

TABLE III—continued
RESPONSE OF MEN TO AQUEOUS PATCHES OF PIPERAZINE HEXAHYDRATE

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Piperazine-BW</th>
<th>Reaction</th>
<th>Score</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L.W.</td>
<td>60</td>
<td>30</td>
<td>Nil locally</td>
<td>0</td>
<td>Rhinorrhea and exacerbation of respiratory symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48</td>
<td>Nil locally</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>J.M.</td>
<td>34</td>
<td>24</td>
<td>Erythema and oedema greater than patch area</td>
<td>3</td>
<td>Recurrence of facial eczema; complained of nocturnal cough</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48</td>
<td>Oedema patch area</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>48</td>
<td>Nil</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>K.D.</td>
<td>38</td>
<td>28</td>
<td>Erythema and oedema greater than patch area</td>
<td>3</td>
<td>Exacerbation of eczema of face and chest</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28</td>
<td>Nil</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>48</td>
<td>Slight oedema patch area</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>48</td>
<td>Nil</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>A.N.</td>
<td>60</td>
<td>30</td>
<td>Erythema greater than patch area</td>
<td>3</td>
<td>Exacerbation of eczema of face and forearms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48</td>
<td>Slight oedema of patch area</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Scoring as for Table I.

**Respiratory Allergenicity** Of the four occupationally exposed and sensitized operatives, one (L.W.) developed respiratory sensitivity to piperazine. He was a 60-year-old man who, up to the age of 55 years, had served in the Australian Regular Army. Until the present episode he had had no serious illnesses, had lead an active life, and had experienced no allergic illness. Between March and June 1964, he mixed 26 batches of sheep drench. By early June he had developed a severe cough with white frothy sputum and a severe wheezing dyspnoea. The dyspnoea was far worse at night and made sleep impossible other than in a sitting position—sleep that was interrupted by bouts of coughing that ended in vomiting. He suffered also from rhinorrhea and excessive lachrymation. He was attended by his private physician and was absent from work intermittently. In December 1964 L.W. insisted that piperazine was the cause of his illness and he was referred to a chest physician. He ceased work for the year on December 23 and his absence from work was
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TABLE IV
RESPONSE OF MEN TO APPLICATION OF AQUEOUS PATCHES OF TWO PREPARATIONS OF PIPERAZINE HEXAHYDRATE CONTAINING 20 G./100 ML.

<table>
<thead>
<tr>
<th>Period of Observation</th>
<th>31 May to 2 June 1965</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject</td>
<td></td>
</tr>
<tr>
<td>S.M.</td>
<td>48</td>
</tr>
<tr>
<td>T.R.</td>
<td>48</td>
</tr>
<tr>
<td>R.N.</td>
<td>48</td>
</tr>
<tr>
<td>S.T.</td>
<td>24</td>
</tr>
<tr>
<td>D.M.</td>
<td>48</td>
</tr>
<tr>
<td>J.M.</td>
<td>48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperazine-K</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hours Patch Worn</td>
<td>48</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Reaction</td>
<td>Nil</td>
<td>Erythema less than patch area</td>
<td></td>
</tr>
<tr>
<td>Score</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperazine-BW</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hours Patch Worn</td>
<td>48</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Reaction</td>
<td>Nil</td>
<td>Erythema less than patch area</td>
<td></td>
</tr>
<tr>
<td>Score</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Scoring as for Table I. J.M. was known to have acquired sensitivity to piperazine hexahydrate; S.T.’s status was uncertain; the other subjects were non-sensitized.

TABLE V
RESPONSE OF NON-SENSITIZED MEN TO APPLICATION OF AQUEOUS PATCHES OF TWO PREPARATIONS OF PIPERAZINE HEXAHYDRATE CONTAINING 25 G./100 ML.

<table>
<thead>
<tr>
<th>Period of Observation</th>
<th>7 to 11 June 1965</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject</td>
<td></td>
</tr>
<tr>
<td>S.M.</td>
<td>48</td>
</tr>
<tr>
<td>T.R.</td>
<td>48</td>
</tr>
<tr>
<td>C.M.</td>
<td>48</td>
</tr>
<tr>
<td>R.N.</td>
<td>48</td>
</tr>
<tr>
<td>N.M.</td>
<td>48</td>
</tr>
<tr>
<td>D.M.</td>
<td>48</td>
</tr>
<tr>
<td>A.B.</td>
<td>48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperazine-K</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hours Patch Worn</td>
<td>48</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Reaction</td>
<td>4 Patch: 2 nil, 2 erythema less than patch area</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score</td>
<td>0 0 1 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperazine-BW</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hours Patch Worn</td>
<td>48</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Reaction</td>
<td>Nil</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>Score</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Scoring as for Table I. The sets of four patches worn by S.M. and T.R. were designed to see if different patch materials appeared to affect the response. They did not.

followed by an abatement and then the disappearance of his symptoms. On January 6 1965, he showed no respiratory abnormality. Auscultation and fluoroscopy were normal, vital capacity was 3.7 l., one-second forced expiratory volume (F.E.V.1.0) 2.7 l. and maximum expiratory flow rate 460 l./min.; blood pressure was 140/80 mm. Hg and the heart was normal.

He returned to work on January 19; on January 21 he noticed some return of his dyspnoea and on the night of January 22 all his symptoms returned. This recurrence had occurred despite the most careful avoidance of piperazine after his return to work. On January 25 auscultation was again normal but vital capacity was only 2.6 l. and the F.E.V.1.0 was 2.2 litres. He was ordered not to return to work and again his symptoms remitted. At this stage it seemed very probable that his condition was a consequence of occupational exposure but it was not clear that piperazine was to blame, especially as he had so carefully avoided all contact with it. On January 29 he was artificially exposed to piperazine-K alone. There was no change in his indices of lung function before and immediately
TABLE VI

<table>
<thead>
<tr>
<th>Period of Observation</th>
<th>Total Patch Test Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean 9 a.m. Effective Temperature</td>
</tr>
<tr>
<td>8–10 Dec. 64</td>
<td>59 deg. F.</td>
</tr>
<tr>
<td>31 May–</td>
<td></td>
</tr>
<tr>
<td>2 June, 65</td>
<td>45</td>
</tr>
<tr>
<td>7–9 June 65</td>
<td>44</td>
</tr>
<tr>
<td>9–11 June 65</td>
<td>35</td>
</tr>
<tr>
<td>22–26 Feb. 66</td>
<td>64</td>
</tr>
</tbody>
</table>

Effective temperature (Lee, 1940) is derived from data supplied by the Commonwealth Bureau of Meteorology. Other data are drawn from Tables I, II, III, and IV.

after exposure but that night he suffered a severe exacerbation of all his symptoms. On the following day he had prolonged expiratory sounds, scattered rhonchi, and fine crepitant rales in both bases. Prednisone was given to terminate the attack. There appears, therefore, no doubt that piperazine hexahydrate was responsible.

Discussion

Piperazine-K and Piperazine-BW A biological difference between two apparently identical preparations of piperazine hexahydrate has been shown to exist, one being much more irritant than the other in non-sensitized subjects. Both were found to conform with the requirements of the B.P. and the U.S.P., and no chemical difference has been detected (Romer, 1965). Chromatography likewise failed to show any impurity in either preparation.

An obvious step was to discover the method of manufacture of the two piperazines since different methods of manufacture might lead to the presence of traces of different intermediate chemicals and thus to the biological difference between the two finished products. This proved to be not so much an obvious step as a long and tortuous road. Ultimately it appeared that both piperazines were the product of the same manufacturer. Thus this attempt to explain the difference between them was unsuccessful.

It is necessary to acknowledge that perhaps there is no real difference. Where p equals 0·01 the likelihood of the observation having been due simply to chance is one in a hundred.

Cutaneous Allergenicity Eczema attributed to piperazine has occurred in workers in the chemical industry in another plant in Sydney, in the United States, in England, in Sweden and, in veterinary surgeons, in South Africa, though, so far as I am aware, the only cases reported have been those occurring in nursing staff (Foussereau, 1963).

Of practical importance is the observation of the effect of environmental temperature on subject response. The cooler the workplace the more safely may piperazine be handled. Indeed, comparison of the experience at Kingsgrove Laboratories with that at the other laboratories suggests that this is a much more important precaution than are the more usual methods of protective clothing, positive-pressure respirators, change of clothing after exposure, etc. In retrospect one can observe that the mixing vat used there was in a much cooler and better ventilated place than that used at Kingsgrove Laboratories.

One manufacturer in the United States has reported that the lower the temperature the less commonly is skin sensitivity observed. This is consistent with the response of the patient J.M. In December 1964, when the effective temperature was 59°F., he responded to a 5 g./100 ml. solution with erythema and vesiculation after 24 hours; but in June 1965, when the effective temperature was 45°F., he was inadvertently exposed to a solution of 20 g./100 ml. and showed no dermal response although he wore the patch for 48 hours. It seems, therefore, that not only the irritancy but also the allergenicity of piperazine varies directly as the environmental temperature.

These observations apply not only to workers handling piperazine in the chemical industry but also to veterinary surgeons and pastoral workers who drench animals with piperazine preparations. It is to be noted that some drenches contain as much as 25 g./100 ml. of piperazine.

Respiratory Allergenicity This case of respiratory sensitivity to piperazine is not unique. Similar cases have occurred in another chemical plant in Sydney and in plants in England and Sweden, although, so far as I am aware, no case has been reported in the medical literature.

The clinical picture is one of lachrymation, rhinorrhea, productive cough, and bronchospasm with onset some hours after exposure to piperazine. This delay of onset is an unusual but constant feature.

The observation in the case of L.W. and the impressions formed in the other cases all favour the view that the piperazine is acting as an allergen rather than as an irritant. Serum from L.W.
sent to the M.R.C. Clinical Immunology Research Group in London but no antibodies were demonstrated; however, it is quite possible that (L.W.'s) reactions are due to reaginic antibody, for which there is no in vitro test. It is very difficult to demonstrate antibodies against small molecular chemical substance' (Pepys, 1966). Pepys has observed a similarly delayed asthmatic response to tuberculin.

It appears that piperazine is a respiratory allergen. At Kingsgrove Laboratories one of seven exposed workers was affected. In another chemical plant in Sydney piperazine, as the carbon disulphide complex, apparently quite commonly gave rise to respiratory sensitivity. In England, where the offending agent is again the carbon disulphide complex, 'exposed persons are not universally affected though the proportion is high'. In Sweden it is said, 'Those having respiratory allergy are by no means peculiar.'

Since piperazine apparently gives rise to this form of respiratory allergy fairly widely, it would be desirable that manufacturers should advise those customers who handle it of the dangers.

I am indebted to the subjects who willingly underwent patch testing and especially to Mr. Les. Wilson who submitted to artificial exposure to piperazine, rightly apprehensive that this would make him sick and well aware that the experiment would confer no benefit upon him; to Dr. Maurice Joseph who saw Mr. Wilson in consultation; to Dr. A. Geoffrey Finley who advised on patch testing; to Dr. J. Pepys who examined Mr. Wilson's serum for antibodies; to Messrs. Boots Pure Drug Ltd. who performed the chromatography; to Messrs. Burroughs Wellcome Ltd. for their very ready co-operation; to numerous other firms of the pharmaceutical industry who provided information essential to this study; and finally to Messrs. Kingsgrove Laboratories Pty. Ltd. who financed this work.

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