blastic anaemia of pregnancy include interference with the utilization of folate, deficient dietary intake of folate, mal-absorption of folate, and increased demand for folate produced by the developing foetus and by lactation. In patients who present with megaloblastic anaemia some months after delivery, interference with the utilization of folate during pregnancy is unlikely to be of importance. The absorption of folic acid, assessed by the serum S. faecalis levels after a test dose of PGA and urinary radioactivity after $^3$H PGA, is usually normal and haematologic response can be induced with small doses of PGA by mouth. However, response to small doses of PGA by mouth is not necessarily indicative of normal absorption by mouth. However, response to small doses of PGA by mouth is not necessarily indicative of normal absorption of natural folate. Sheehy et al. noted response to small doses of PGA in patients with tropical sprue who had failed to respond to a diet containing more than 1 mg of 'folic acid-like activity' by assay. As the bulk of the folate activity in the diet is in the conjugated form. Sheehy et al. suggested that this natural material may be of little value to man. In the aetiology of megaloblastic anaemia following pregnancy, it is possible that conjugate activity and thus ability to absorb natural folate may be disturbed. However, the response to natural folate in the present patient makes a conjugate defect unlikely and suggests rather that the folate content of the diet is inadequate to induce haematologic remission. The finding also suggests that the syndrome can best be explained on the basis of deficient dietary folate intake associated with the increased demands for folate produced by pregnancy and lactation.

The consumption of adequate quantities of unprepared green leafy vegetables, during pregnancy and lactation, appears of major importance in the prevention of megaloblastic anaemia.

**SUMMARY**

In a patient with megaloblastic anaemia following pregnancy, haematologic remission was induced by oral administration of natural folate in the form of lettuce. Subsequent administration of synthetic folic acid failed to induce a secondary reticulocyte response. The importance of dietary folate deficiency in the pathogenesis of this form of megaloblastic anaemia is emphasized.

We wish to thank the Director, South African Institute for Medical Research, for facilities to carry out this study; the Superintendent, Baragwanath Hospital, for permission to publish the case; Misses V. Brandt and P. Welch for technical assistance, and Drs. M. Schwartz, L. Shamroth, R. Cassel and H. Blumberg for their help.

**REFERENCES**


**THE AETIOLOGY OF MILIARIA**


Prickly heat (miliaria rubra) is an important cause of morbidity in the gold mines of South Africa and there is evidence that its incidence is rising with the increase in deep-level mining and the hotter underground conditions in the Orange Free State. A similar high incidence is seen in miners after years of free-living in the tropical climate of the Orange Free State. A similar high incidence is seen in miners after years of free-living in the tropical climate of the Orange Free State.

In a patient with megaloblastic anaemia following pregnancy, haematologic remission was induced by oral administration of natural folate in the form of lettuce. Subsequent administration of synthetic folic acid failed to induce a secondary reticulocyte response. The importance of dietary folate deficiency in the pathogenesis of this form of megaloblastic anaemia is emphasized.

As its victims are chiefly senior, experienced miners who have no alternative trade or skill, chronic miliaria represents a considerable hardship to the sufferer and a loss to the industry. It is this variety, therefore, which forms the subject of the present enquiry.

**CLINICAL MATERIAL**

Particulars relating to the last 50 consecutive cases of chronic miliaria are presented. Many items are not capable of comparison with unaffected workers; thus we do not know how many unaffected men experience a change in working conditions each year; we are ignorant of the average age of the population at risk, of the proportion of dark to fair skins, of slender to obese, and of several other data. We can, however, analyse differences within the group, and certain conclusions will be derived from these.

The average age was 37·3 years (youngest 21, oldest 53) and the period of underground work before the onset of prickly heat, excluding a possible transient attack near the beginning of their mining career, varied from 3 to 35 years, with an average of 13·4. No particular physical type
seemed to be either especially prone to, or exempt from, the disease. **AETIOLOGICAL FACTORS**

1. **Environmental**

   Of the patients 23 (46%) dated the onset of their prickly heat to a change in working conditions, i.e. to surroundings in which wet-bulb temperatures were higher or ventilation less efficient. Developing ends were especially incriminated, because of the absence of through ventilation.

   The majority of new cases are seen in the summer months; the relative freedom during the winter may presumably be compared with the lower incidence of prickly heat in the tropics when air conditioning has been introduced in workers' sleeping quarters8,6 and seasonal differences noted by Kuno.7

2. **Cutaneous**

   In view of O'Brien's contention14,15 that staphylococcal infection is a major aetiological factor, a history of previous pyoderma was sought in each case; 8 patients had been thus affected. In a further 5, prickly heat had supervened on recovery from an eczema; of these, 4 were caused by cement. It will be recalled that Sulzberger and Herrmann2 have listed a number of common antecedent dermatoses in subjects of prickly heat.

3. **Systemic**

   In a previous paper8 the role of stress (in the sense given by Selye) was briefly mentioned; it was first mooted by Ladan11 and the concept expanded by Sargent and Slutsky,12 in a closely reasoned exercise in inductive logic. The causes of such stress in our population may be conveniently classified into psychic and somatic.

   (a) **Psychic.** Mining, in spite of increasing vigilance and strict supervision, is a hazardous occupation. Though the risks are known and accepted by the underground miner as an inevitable part of his occupation, we have the impression that the more imaginative may experience feelings of apprehension, which may lower tolerance to heat.

   (b) **Somatic.** Physical trauma preceded the onset in 5 cases. A typical example is the following: G.V., aged 54 yrs. Underground miner for 22 years. In 1959 was hurt in a rock fall, sustaining a fracture of the clavicle and several ribs. Complete physical recovery and return to work in the same surroundings after 7 weeks. Three days later prickly heat developed and recurred promptly at each attempt to resume underground work. He states that each working shift since the accident brings on feelings of apprehension. A biopsy (P67), serially sectioned, showed the diagnostic appearances of miliaria rubra.

   Other forms or evidence of stress encountered included 2 cases of peptic ulcer of the duodenum, heat exhaustion, a so-called 'heart attack', second stage silicosis and infective hepatitis. Included under factors which are liable to cause loss of acclimatization is absence from work, owing to vacation; 2 such were noted. It is of course possible that part or all of the effect of trauma is accounted for by the enforced absence from conditions of heat and humidity and consequent loss of acclimatization, though it must be conceded that the annual month's holiday had not previously produced the disease in these patients.

   The severity of the cases was assessed clinically from the extent and intensity of the rash and from its liability to recurrence. The first Table shows the distribution of antecedent, possibly precipitating factors in the groups severely and less severely affected. In those patients in whom more than 1 possible factor was operative all are listed. An antecedent occurrence could be found in 41 out of the 50 cases and the distribution of such occurrences (with the exception of 'other stress') is fairly even.

   We can see (Table I) that 23 out of the 50 subjects dated the onset of their chronic miliaria to a change for the worse in their working conditions. If we regard this in itself as a sufficient cause it is of interest to compute the incidence of other factors in the 2 groups thus defined (Table II).

   **TABLE I. COMPARISON OF CASES IN RESPECT OF SEVERITY**

<table>
<thead>
<tr>
<th>Antecedent conditions</th>
<th>Severe (23)</th>
<th>Not severe (27)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (yrs)</td>
<td>40</td>
<td>38</td>
<td>37.7</td>
</tr>
<tr>
<td>Average years underground work</td>
<td>14.7</td>
<td>11.1</td>
<td>13.4</td>
</tr>
<tr>
<td>Change in working conditions</td>
<td>11</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Pyoderma</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Eczema</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Trauma</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Other stress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After vacation</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

   From this it is seen that those who had developed miliaria soon after changing their working conditions were slightly younger, and had rather less underground service than the rest. Consideration of the last 4 items shows that about half the patients who had no change in their working conditions showed stress and/or absence from work whereas less than a quarter of the others showed these factors. Where climatic conditions remain constant, therefore, there is a greater tendency for some cutaneous or other factor to precede miliaria; this is not surprising. We regard the climatic factors as a specific and precipitating cause, others as less specific.

   **DISCUSSION**

   **Microbial Agents**

   O'Brien14,15 and Lyons et al.16 maintain that staphylococcal infection is the prime cause of miliaria. Our figures show that only 16% (Table I) suffered from preceding pyogenic infection of the skin; a further 30%, however, developed cutaneous sepsis after suffering from miliaria for some time. We regard this as a complication of scratching, comparable to another 18% who drifted from miliaria into chronic eczema. Perhaps the most powerful argument against O'Brien's hypothesis is the almost invariable absence of polymorphonuclear leukocytes at the site of the miliaria lesion where a purely lymphocytic infiltrate is the rule. Of over 500 eccrine sweat-units examined by us we regard this in itself as a sufficient cause.

   **Mechanical Obstruction**

   The presence of a keratotic or parakeratotic plug in the ostium, and consequent dilatation with or without rupture of the sweat duct, appears to be a secondary manifestation in our cases. As mentioned previously, Sulzberger and Herrmann2 have demonstrated that other dermatoses, notably atopic dermatitis, atebria eruptions and the condition described by Sulzberger and Garbe may be followed by miliaria; in such cases the ostial plug is the result of the
Further work has shown that the chronic use of these cases; we cannot say how many in- solutions, further increases, and left-ventricular coronary blood flow. The assumption that coronary sinus drainage has recently been questioned. 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.

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 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 being the cause of elevated sweat chloride, and the concept of prickly heat being a stress in the sense given to the term by Selye. 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, also produces an alteration in the cellular sodium-potassium ratio consequent on the breakdown of glycogen, and even allergens may have to be considered. The search continues.

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REFERENCES

Prenylamine ("Segontin") in prophylaxis of angina pectoris attacks

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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.