Phenacetin-induced haemolytic anaemia

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SYNOPSIS  Haemolytic anaemia, rarely severe, is a common yet often unrecognized complication of the prolonged use or abuse of phenacetin-containing analgesics. Irregularly contracted (pyknocytes) or fragmented erythrocytes (schistocytes) are commonly present in the peripheral blood in this form of anaemia. It is emphasized that their recognition during screening of blood films may reveal patients previously unsuspected of analgesic abuse and at a stage before the development of the more serious complication of nephropathy. Fourteen such patients, detected during the last 18 months, are briefly described and the pathogenesis and laboratory features of the anaemia reviewed.

Phenacetin, introduced into clinical medicine in 1887, remains a popular constituent of antipyretic analgesics in this country. At least 86 such preparations, all available to the general public without prescription, are listed in Martindale's Extra Pharmacopoeia (1968).

The excessive consumption of such preparations has been long recognized to produce several toxic effects on the haemopoietic system, especially toxic haemolytic anaemia. This complication, including its prevalence, has commanded scant attention in recent years during which time most interest has centred on the more serious complications of renal papillary necrosis and non-obstructive pyelonephritis (Lancet, 1968). Haemolytic anaemia induced by phenacetin may be acute or chronic in type. The former, which is extremely rare, may occur in the presence of red cell glucose 6-phosphate dehydrogenase deficiency (Houston and Barlow, 1959; Gilles and Ikeme, 1960; Wong, 1961; Harley and Robin, 1962) or a drug-red-cell immune mechanism (Muirhead, Halden, and Groves, 1958; MacGibbon, Loughridge, Hourihane, and Boyd, 1960; Dausset and Contu, 1964). The anaemia may follow the ingestion of only a small dose of the drug, is usually severe, and may be accompanied by intravascular haemolysis, haemoglobinuria, and anuria.

In contrast, the chronic form is much more common and results from the habitual ingestion of the drug. The degree of anaemia is usually mild but may be progressive and severe if other potentiating factors are present. Characteristically, the blood film shows (Fig. 1) a variable number of pyknocytes (irregularly contracted erythrocytes), schistocytes (fragmented erythrocytes) and spherocytes, excessive polychromasia, and occasionally punctate basophilia. In addition, Heinz bodies may be demonstrable and methaemoglobin or sulphaemoglobin may be detected spectroscopically.

Investigation

Over a period of 18 months, 14 patients all previously unsuspected of prolonged self-medication with phenacetin-containing analgesics were dis-

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covered following the recognition of pyknocytes and schistocytes in routine blood films.

During this study approximately 18,000 sequestre blood samples, accompanied by two freshly spread films, were submitted by general practitioners in the N.E. region of Scotland for routine haematological investigation which consists of estimation of haemoglobin, microhaematocrit, mean corpuscular haemoglobin concentration, total and differential white cell counts, and examination of a Leishman-stained film. If the characteristic morphological features of 'toxic' red cell damage were found in the film, the following additional tests were carried out: reticulocyte count, supravital staining for Heinz bodies, direct antiglobulin test, screening for glucose 6-phosphate dehydrogenase deficiency, estimation of plasma urea, and spectroscopy for methaemoglobin and sulphaemoglobin.

Those patients showing evidence of a toxic haemolytic anaemia but who were known to be taking phenacetin-containing analgesics or sulphophamide preparations prescribed by their family doctor were excluded from the present study. Of 17 patients suspected of analgesic abuse on haematological grounds alone, 14 subsequently admitted to the habitual ingestion of phenacetin-containing preparations, the type and amount being given in Table I.

**Results**

The main laboratory findings are given in Table I. All the patients were females. None were found to have glucose 6-phosphate-dehydrogenase deficiency or a positive direct antiglobulin test. None had renal insufficiency as assessed by plasma urea estimation.

### Table I

**Laboratory results**

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age</th>
<th>Hb (g/100 ml)</th>
<th>MCHC (%)</th>
<th>WBC (c mm)</th>
<th>Reticulocytes (%)</th>
<th>Meth-</th>
<th>Sulph-</th>
<th>Heinz</th>
<th>Plasma Urea (mg/100 ml)</th>
<th>Analgesic Consumption</th>
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<tr>
<td>1</td>
<td>44</td>
<td>9.8</td>
<td>28.8</td>
<td>15,600</td>
<td>4.0</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>35</td>
<td>10/Codis 18 mth</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>9.9</td>
<td>32.4</td>
<td>7,000</td>
<td>3.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>22</td>
<td>4-6/Codis 1-2 yr</td>
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<tr>
<td>3</td>
<td>70</td>
<td>11.6</td>
<td>31.4</td>
<td>7,800</td>
<td>2.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>4-6/Tab. 15 mth</td>
</tr>
<tr>
<td>4</td>
<td>82</td>
<td>8.6</td>
<td>27.9</td>
<td>6,500</td>
<td>7.0</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>20</td>
<td>4-6/TAB. 18 mth</td>
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<td>5</td>
<td>28</td>
<td>8.6</td>
<td>29.6</td>
<td>5,300</td>
<td>4.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>28</td>
<td>4-6/A.P.C. 1 yr</td>
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<tr>
<td>6</td>
<td>61</td>
<td>10.1</td>
<td>32.5</td>
<td>7,000</td>
<td>2.6</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>25</td>
<td>4-6/Cod.Co. 1 yr</td>
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<tr>
<td>7</td>
<td>44</td>
<td>11.0</td>
<td>31.4</td>
<td>10,000</td>
<td>3.4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>32</td>
<td>10-12/TAB. 1-2 yr</td>
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<tr>
<td>8</td>
<td>33</td>
<td>9.8</td>
<td>28.8</td>
<td>11,700</td>
<td>4.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>25</td>
<td>2-6/A.P.C. 2 yr</td>
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<tr>
<td>9</td>
<td>82</td>
<td>12.0</td>
<td>31.4</td>
<td>6,600</td>
<td>3.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>32</td>
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<tr>
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<td>84</td>
<td>8.3</td>
<td>30.2</td>
<td>5,100</td>
<td>5.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>28</td>
<td>Many yr 30 yr</td>
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<tr>
<td>11</td>
<td>52</td>
<td>10.1</td>
<td>33.6</td>
<td>7,200</td>
<td>4.8</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>26</td>
<td>2-4/A.P.C./Codis</td>
</tr>
<tr>
<td>12</td>
<td>33</td>
<td>11.2</td>
<td>30.3</td>
<td>7,400</td>
<td>4.2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>31</td>
<td>4-6/Codis 2 yr</td>
</tr>
<tr>
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<td>41</td>
<td>6.6</td>
<td>25.4</td>
<td>11,800</td>
<td>24.0</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>35</td>
<td>6-10 Codis/Aspro 9 yr</td>
</tr>
<tr>
<td>14</td>
<td>68</td>
<td>8.2</td>
<td>30</td>
<td>9,500</td>
<td>8.0</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>35</td>
<td>4-10 Codis/Aspro 9 yr</td>
</tr>
</tbody>
</table>

Case 13

This patient was admitted to hospital for further investigation because of the severity of the anaemia and the presence of ankle oedema, and is described in greater detail because of some unusual features. Clinical examination showed mucosal pallor and pitting oedema of both ankles. The heart was not enlarged but a systolic murmur was audible in all areas, loudest along the left sternal border. The chest was clinically and radiologically normal. The spleen was palpable two fingerbreadths below the left subcostal margin. Laboratory investigations: haemoglobin was 6·6 g per 100 ml; PCV 26%; MCHC 25·4%; reticulocytes, 24%; WBC 11,800 per cmm with 79% neutrophilcs. The blood film showed moderate erythroanisocytosis with hypochromia, a large number of pyknocytes, schistocytes, and spherocytes, excessive polychromasia, and 3 late normoblasts per 100 white cells. A small number of orthochromic red cells contained solitary Howell-Jolly bodies. Platelets were numerically normal. Supravital staining revealed numerous Heinz bodies but no methaemoglobin or sulphaemoglobin was detected on spectroscopy. Sternal marrow examination was normal apart from moderate normoblastic hyperplasia associated with increased Howell-Jolly body formation. Serum iron was 50 μg per 100 ml and TIBC 335 μg per 100 ml. Liver function tests, plasma urea, serum folate, and vitamin B₁₂ levels were normal. The direct antiglobulin test was negative and no autoagglutinins were detected at 4°C or 20°C. The urine gave a trace reaction for both protein and urobilinogen while occasional pus cells were found on microscopy of the centrifuged de-
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posit. Stool examination was repeatedly negative for occult blood.

The patient admitted that during the previous three years she had regularly consumed six-10 Codis or Veganin tablets daily for headaches, menstrual pain, and 'rheumatics.' She was treated with oral iron alone and when she was discharged 14 days later the haemoglobin was 8·6 g per 100 ml and reticulocytes 8 %. She was seen as an outpatient one month later, when the haemoglobin was 9·9 g per 100 ml and reticulocytes 10 %. Although she strongly denied having taken analgesics of any kind after her discharge from hospital, schistocytes and pyknoocytes were again quite numerous in the blood film and the plasma salicylate level was found to be 18 mg per 100 ml.

CASE 14
This patient was also admitted to hospital for investigation of a concomitant macrocytic blood picture. She was found to have transitional megaloblastic haemopoiesis due to folate deficiency, the serum and red cell folate levels being 1·2 μg and 143 μg per 100 ml respectively. This patient, in addition to consuming large quantities of phenacetin-containing analgesics, was addicted to alcohol and barbiturates.

Discussion
In man, the major part of phenacetin is de-ethylated, chiefly in the liver, to N-acetyl-p-aminophenol (NAPA, paracetamol) which is then conjugated and excreted in the urine (Brodie and Axelrod, 1949). Paracetamol appears to be free of haematotoxic effects. A minor fraction, however, is deacetylated to p-phenetidin and this metabolite or one of its breakdown products is thought to be responsible for inducing the red cell damage, including methaemoglobin formation (Brodie and Axelrod, 1949). Similar changes may also be caused by acetil-4-chloranililide (A4CA), a contaminant found in phenacetin (Schnitzer and Smith, 1966).

Pathogenesis of the Anaemia
The main features of the chronic haemolytic anaemia induced by phenacetin are an alteration in red cell morphology and permeability; the formation of methaemoglobin and/or sulphaemoglobin; and the formation of Heinz bodies.

The pathogenesis of these changes induced by p-phenetidin and its metabolites or A4CA is not firmly established but all may be explained on the basis of oxidative injury.

Effect on the red cell membrane
As potent oxidants, these substances are likely to possess a strong affinity for the thiol (SH) groups of the red cell membrane. The importance of membrane SH activity in maintaining the integrity and viability of the red cell is well recognized (Jacob and Jandl, 1962a and b) and hence any impairment of this function may account for the contraction, sphering, distortion, and fragmentation of the red cells.

Although the process of red cell fragmentation and erythroclasis is assumed to be part of the normal mechanism of red cell destruction and elimination in health (Rous and Robertson, 1917), irregularly contracted or fragmented cells are seldom seen in films of normal blood. When present in appreciable numbers they usually denote red cell 'damage' and a haemolytic process. The 'damage' may be induced by various physical factors as in severe burns, extracorporeal circulations, reconstructive cardiac surgery, or micro-angiopathic states but more commonly it results from the toxic action of chemicals or drugs. I have found that phenacetin, salicylazosulphapyridine (Salazopyrin), and sulphamethoxypyridazine (Lederkyn) are the drugs most commonly implicated.

Methaemoglobin and sulphaemoglobin formation
p-Phenetidin and its metabolites, again in the role of direct or indirect oxidants, are likely to impose severe stress on the methaemoglobin reductase systems of the red cell with resultant toxic methaemoglobin-anaemia. The latter, as shown in this series, is not a constant feature in patients subjected to the prolonged use of phenacetin. This anomaly has so far eluded satisfactory explanation but it is suggested that it may be related to a decline in functional activity of the reductase enzyme systems with increasing red cell age. Thus, on initial exposure to the drug only the oldest cells may be susceptible to excessive or irreversible methaemoglobin formation and following their elimination the remaining younger red cell population may be able to resist the oxidative challenge of the drug. A similar explanation has been postulated to account for the well recognized dissociation between methaemoglobin formation and haemolysis in the analogous primaquine-induced haemolytic anaemia (Beutler, 1962; Brewer, Tarlov, Kellermeyer, and Alving, 1962). This view would appear to gain support from the findings in case 13 of the present series, where no methaemoglobin was detected in the presence of an unusually severe and active haemolytic process, and the suggestion of Ross and Ciccarelli (1962) that the apparent sensitivity of infants to phenacetin may be related to an inadequacy of the methaemoglobin reduction mechanisms in the red cells of normal infants.

Heinz body formation
These erythrocyte inclusion bodies may be regarded
as representing the end product of oxidative denaturation of haemoglobin, but again they are not an invariable accompaniment of phenacetin-induced anaemia. Thus Jasinski and Müller (1950) reported their presence in two of three cases, Wuhrmann and Jasinski (1955) in eight of 15, and Marti (1958) in one of 20 cases. In these instances there was no correlation between the severity of the anaemia and the proportion of red cells containing Heinz bodies. In this connexion it is pertinent that Selwyn (1955) not only revealed the potential haemotoxicity of phenacetin but also the important role of the spleen in removing Heinz bodies from the circulation, when he demonstrated that these bodies regularly appeared in the blood of splenectomized patients given a normal therapeutic dose of the drug.

**POTENTIATING AND MODIFYING FACTORS**

The severity of the anaemia may be potentiated and the characteristic peripheral blood appearances modified by factors relating to an underlying disease for which the drug is being taken, eg, rheumatoid arthritis, or other complications of analgesic abuse, including alimentary blood loss, renal damage, and marrow hypoplasia.

Thus significant hypochromia was observed in eight of the 14 patients described and in these cases the degree of anaemia was found to be greater and the reticulocyte count higher than in the remainder of the series. Although none of the present patients were found to have impaired renal function, as assessed by plasma urea estimation, previous radiochromium studies have revealed that in its presence the reduction in red cell survival is exaggerated (Fris, Fogh, and Nissen, 1960) and that haemolysis occurs mainly in the spleen (Lorenzen and Schwartz, 1960). None of the present series of patients showed evidence of marrow hypoplasia and pancytopenia (Wijnja, Snijder, and Nieweg, 1966; Dawborn, Fairley, Kincaid-Smith, and King, 1966) or exhibited the uncommonly reported feature of sideroblastic change (Dacie and Mollin, 1966; McMillan, Lawson, Paton, and Linton, 1968). Macrocytosis, apparently unrelated to vitamin B₁₂ or folic acid deficiency but attributed without explanation to the abuse of both phenacetin and salicylate, has been noted by several observers (Jasinski and Müller, 1950; Prescott, 1966; Wijnja et al, 1966). In contrast the one patient in this series exhibiting macrocytosis was found to have a megaloblastic marrow and folic acid deficiency attributable to a poor diet augmented by addiction to alcohol and barbiturates.

Finally, it has been questioned whether the haematoxicity of phenacetin-containing preparations may be potentiated, in some unknown way, by the coexistence of gastrointestinal lesions, particularly partial gastrectomy, the blind loop syndrome, and malabsorption (Hutchison, Jackson, and Cassidy, 1962; Dacie and Mollin, 1966). Could it be that higher blood concentrations of p-phenetidin and its toxic metabolites are attained under these circumstances by an alteration in the route of metabolism of the drug? Our knowledge of factors influencing this process in man is extremely limited, and it may very well be that their detailed study by more sophisticated methods, including pharmacogenetics, may help to explain some of the apparent anomalies and variations in both the pattern and degree of the drug's toxicity.

**PREVALENCE OF ANALGESIC ABUSE**

The prevalence of analgesic abuse and its consequent dangers have long been recognized in Sweden, Denmark, and Switzerland where for several years phenacetin has only been available by prescription. In contrast, little is known about its prevalence in Britain. This study and three recently published surveys of analgesic nephropathy (Prescott, 1966; McMillan et al, 1968; Bell, Kerr, Swinney, and Yeates, 1969) have however indicated that it is not uncommon, particularly in middle-aged females.

The observation that none of the present patients were clinically suspected of analgesic abuse would appear to indicate that the magnitude of the problem may be largely underestimated, if not unrecognized, because of the difficulties of knowing when to suspect and how to confirm the diagnosis. Hence in the absence of a clear-cut clinical syndrome of analgesic abuse (Gault, Rudwal, and Redmond, 1968), it is advocated that scrutiny of the peripheral blood film by an experienced observer may be a very useful screening test.

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**References**


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