THE HYPERSENSITIVITY REACTIONS TO PARA-AMINOSALICYLIC ACID (P.A.S.)

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Para-aminosalicylic acid (P.A.S.) was first used in 1946 for the treatment of tuberculosis by Lehmann (1946). With the exception of nausea and vomiting, which Lehmann himself described, it was at that time thought that the drug was free from side-effects. However, with its increasing use, reports of other toxic reactions began to appear (Nagley and Logg, 1949; Hemming and Stewart, 1949) and there now exists an extensive literature on the subject.

These reactions fall into three groups (Dixon, 1954). First is a natural intolerance to the drug which as many as 58% of patients (Medical Research Council, 1950) experience, whose manifestations (nausea, vomiting and sometimes diarrhoea) appear very soon after starting the treatment.

Secondly, pharmacological side-effects have been described. These consist of hypoprothrombinaemia (Swanson, 1949), hypokalaemia (Cayley, 1950), hypothyroidism (Komrower, 1951) and hyperthyroidism (Tandhanand and Buri, 1956). The alterations in thyroid metabolism are usually associated with the occurrence of a goitre.

Thirdly, there are the hypersensitivity reactions, and these are usually the most serious. Table 1 lists these reactions.

Kniest (1952) has reported an anaphylactic reaction immediately after restarting treatment in two cases that had already shown some allergy to P.A.S., but this should be regarded as an exaggerated version of the normal hypersensitivity reaction.

The present case is reported because it shows so many of the hypersensitivity reactions to P.A.S., and helps to shed some further light on them. In addition, ascites and pleural effusion have not previously been reported as complications of P.A.S. therapy. Furthermore it is the first report of P.A.S. sensitivity following the administration of calcium B-P.A.S.

Calcium 4-Benzamidosalicylate (Calcium B-P.A.S. "Therapas")

In an attempt to overcome the high degree of intolerance found when P.A.S. is administered as the normal sodium or calcium salt (in solution, in cachets or in granules), Bavin and James (1953) described this new substance which is insoluble and, perhaps for that reason, tasteless. It is broken down in the body to liberate P.A.S. and benzoic acid. Preliminary reports suggest that calcium B-P.A.S. is therapeutically as effective as the normal salts of P.A.S., and produces intestinal disturbances in a far smaller proportion of cases.

Case Report

The patient, a girl of 7 years, developed primary tuberculosis and was treated with I.N.H. and calcium B-P.A.S. There was nothing relevant in either her previous medical history or in her family history. Her

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### Table 1

THE HYPERSENSITIVITY REACTIONS TO P.A.S.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Cuthbert (1950)</td>
</tr>
<tr>
<td>Skin rashes</td>
<td>Horne (1949)</td>
</tr>
<tr>
<td>Exfoliative dermatitis</td>
<td>Cuthbert (1950)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Steel (1952)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>Jeffery et al. (1952)</td>
</tr>
<tr>
<td>Headache</td>
<td>Hemming and Stewart (1949)</td>
</tr>
<tr>
<td>Lachrimation and conjunctivitis</td>
<td>Warring and Howlett (1952)</td>
</tr>
<tr>
<td>Blood dyscrasias</td>
<td></td>
</tr>
<tr>
<td>(a) Eosinophilia</td>
<td>Dixon (1954)</td>
</tr>
<tr>
<td>(b) Glandular fever cells</td>
<td>Cannemeyer et al. (1955)</td>
</tr>
<tr>
<td>(c) Agranulocytosis</td>
<td>Muri (1952)</td>
</tr>
<tr>
<td>Vasomotor rhinitis</td>
<td>'Any Questions' (1953)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Cuthbert (1950)</td>
</tr>
<tr>
<td>Hepatitis and hepatomegaly</td>
<td>Dixon (1954)</td>
</tr>
<tr>
<td>Albuminuria and haematuria</td>
<td>Nagley and Logg (1949)</td>
</tr>
<tr>
<td>Transient anuria</td>
<td>Cuthbert (1950)</td>
</tr>
<tr>
<td>Anaphylactic shock</td>
<td>Kniest (1952)</td>
</tr>
<tr>
<td>Angioneurotic oedema</td>
<td>Cuthbert (1950)</td>
</tr>
<tr>
<td>Laryngeal stridor</td>
<td>Warring and Howlett (1952)</td>
</tr>
<tr>
<td>Intractable cough</td>
<td>Kniest (1952)</td>
</tr>
<tr>
<td>Asthma</td>
<td>Cuthbert (1950)</td>
</tr>
<tr>
<td>Löffler's syndrome</td>
<td>Warring and Howlett (1952)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Hemming and Stewart (1949)</td>
</tr>
<tr>
<td>Ascites</td>
<td>Gerrits (1951)</td>
</tr>
<tr>
<td>Asbest</td>
<td>Warring and Howlett (1952)</td>
</tr>
<tr>
<td>Present case</td>
<td></td>
</tr>
</tbody>
</table>

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**Note:** The table lists various side-effects associated with the use of P.A.S., including fever, skin rashes, exfoliative dermatitis, pruritus, stomatitis, headache, blood dyscrasias, vasomotor rhinitis, lymphadenopathy, hepatitis and hepatomegaly, albuminuria, transient anuria, anaphylactic shock, angioneurotic oedema, laryngeal stridor, intractable cough, asthma, Löffler's syndrome, pleural effusion, and ascites. The references are cited for each reaction, with the most recent studies listed first. The table also includes calcium 4-Benzamidosalicylate (Calcium B-P.A.S. "Therapas"), which was introduced as a more tolerable alternative to P.A.S. It is discussed in the context of its therapeutic effectiveness and reduced side-effects compared to the normal salts of P.A.S. The case report describes a 7-year-old girl with primary tuberculosis treated with I.N.H. and calcium B-P.A.S., with no relevant history.
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elder brother (the only sibling) and both her parents were
well and showed no evidence of active tuberculous
infection: the contact was never found.

For convenience all dates have been related to the day
she first received P.A.S. ('P' day, April 24). Fig. 1
illustrates the progress of the case.

31.3.56  The patient was seen with a rash on her shins
(P−24) which resembled erythema nodosum.
2.4.56  Tuberculin jelly test positive, control negative.
4.4.56  Radiological report (1).
5.4.56  Erythema nodosum settling slowly. A fairly
constant evening pyrexia of 99°F. noted.
20.4.56  Radiological report (2)
24.4.56  In view of the increasing radiological changes,
anti-tuberculosis therapy was started, using
I.N.H. and 'calcium B-P.A.S.'.
20.4.56  A rubella-like eruption appeared during the
afternoon but lasted only two hours. Its
significance was not appreciated.
12.5.56  The eruption recurred, and with it the tempera-
ture rose to 101°F. The cervical nodes,
especially those in the posterior triangles, were
enlarged.
14.5.56  For the first time nausea was experienced on
taking the B-P.A.S. The dose was reduced
with no improvement.
17.5.56  The child's condition was much worse, and
she looked ill. An irritating morbilliform
rash had replaced the rubella-like one and
covered the whole body. The conjunctivae
were suffused and her eyes were watering.
Several small ulcers were present on the
buccal mucosa and inside the mouth. The
adenitis had increased considerably; not only
were all the nodes in the neck enlarged, but
also those in the axillae and groin, though
the spleen could not be felt (nor could it at any
other time). All anti-tuberculosis therapy was
stopped on this day.

The eyelids and face were swollen and the
ankles slightly oedematous. She was com-
plaining of quite severe abdominal pain and
on examination the liver edge was palpable
and tender. The urine showed the presence
of bile salts and pigments, and there was
albumin + + (bed-side analysis).

Liver edge palpable three fingerbreadths below
the costal margin. Temperature 101-104°F.
Pathological report (3)

The temperature returned to normal, but the
liver was now palpable five fingerbreadths and
jaundice could be detected, though it was not
at any time very marked.

Subjectively the child felt much better but on
examination signs were detected in the chest
for the first time. The percussion note was

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Fig. 1.

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dull in the right axilla and air entry was diminished over the right lower lobe.

29.5.56 Radiological report (3)
(P+35) Pathological report (4)
30.5.56 Ascites was found. The skin was beginning to peel over both thumbs and thenar eminences as the rash was starting to fade.
(P+36) 2.6.56 General condition much improved. Liver edge decreased to two fingerbreadths. Ascites was now no longer detectable. The oedema had subsided. Pulmonary signs were unaltered. The exfoliation was spreading all over the body.

4.6.56 The chest was clinically clear. The oral and conjunctival ulcers had settled. The adenitis was subsiding.

5.6.56 Radiological report (4)
(P+42) Pathological report (5)
12.6.56 All the signs had disappeared except for the remains of the exfoliative process on the legs.
(P+49) 29.6.56 Child clinically very well. Appetite good.
(P+66) Up half day.
Radiological report (5)
Pathological report (6)

14.8.56 Gaining weight. Full activity.
(P+112) Radiological report (6)
Pathological report (7)
11.10.56 Radiological report (7)
(P+140) Pathological report (8)
1.10.56 Permitted to return to school.
(P+161)

10.9.57 The child is clinically very well. The primary tuberculosis complex is no longer visible radiologically.

**Radiological Reports**

1. 4.4.56 Lung fields clear. Left hilum a little suspicious.
2. 20.4.56 The left hilar glands are enlarged and there is some consolidation in the apical segment of the lower lobe or in the posterior segment of the upper lobe. The radiological appearances are consistent with the presence of a primary tuberculous complex.

3. 29.5.56 There is now a small effusion at the right base and some fluid is also present in the intralobar fissure. There may be a little atelectasis above it (Fig. 2).
4. 5.6.56 The right lung field is now clear and there is no evidence of fluid. The left hilar mass is unchanged (Fig. 3).
5. 29.6.56 The position of the left hilum has not altered materially.
6. 14.8.56 Comparison with the previous films shows little change. The left hilar glands are still enlarged.
7. 11.9.56 The enlarged glands at the left hilum have not altered materially in size in the last month.

**Pathological Reports**

1. 4.4.56 Hb 11.2 g. %, W.B.C. 7,600 per c.mm. (5,800 polymorphs, 1,700 lymphocytes, 100 monocytes). E.S.R. 42 mm./hr.
2. 20.4.56 Hb 12-8 g. %, W.B.C. 13,000 per c.mm. (8,400 polymorphs, 3,900 lymphocytes, 700 monocytes). E.S.R. 41 mm./hr.
3. 23.5.56 Hb 12-3 g. %, W.B.C. 9,000 per c.mm. (3,500 neutrophils, 500 eosinophils, 5,000 lymphocytes). A few of the mononuclear cells were atypical and resembled those seen in glandular fever.
4. 29.5.56 Urine: amber yellow. S.G. 1.016, pH 7-0, albumin nil, bile salts nil, glucose nil, bile pigments ++, urobilinogen 1.5 units %, 6 leucocytes and less than 1 R.B.C. per c.mm.
5. 5.6.56 Hb 12-7 g. %, W.B.C. 13,000 per c.mm. (7,600 polymorphs, 6,300 lymphocytes, 600 monocytes). E.S.R. 24 mm./hr. Urine: bile salts +, bile pigments ++, urobilinogen 1.1 units %. A few of the monocytes were atypical. Paul-Bunnell test was positive to 1:16 only, i.e., negative.
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Stomatitis and conjunctival suffusion together with a puffy face and generalized oedema are typical of a drug fever, and albuminuria is often found in the same condition. The rash, too, which resembled erythema multiforme, can occur with a drug fever, and, as mentioned above, it also often accompanies the hepatitis and 'glandular fever reaction' following P.A.S.

Allergic reactions to P.A.S. therapy are not common in children (Todd, 1953) though they do suffer the same natural intolerance to the drug. Hepatitis does not appear to have been reported previously in a child though Oppe (personal communication) had a case which ended fatally. Both of Kniest's (1952) cases of anaphylactic reaction were in children, the older of whom (aged 12) died from a concomitant flare-up of a tuberculous infection.

Summary

A case is reported of a child treated with P.A.S. who developed hypersensitivity reactions. These reactions included drug fever, lymphadenopathy with 'glandular fever cells' in the blood, hepatitis with jaundice and dermatitis with exfoliation. In addition the child developed Löfler's syndrome with a pleural effusion and had ascites.

I wish to thank Drs. J. Fielding and P. L. Masters for the pathological reports and Drs. T. R. Riley and J. J. Stevenson for the radiological reports.

Considerable advice was received from the St. Mary's Hospital Home Care Department, though, because the patient lived outside the area they cover, she did not come into their scheme. I would like to thank Dr. Lightwood and his team for all their assistance, and in particular I wish to thank Dr. Lightwood for his help in the preparation of this paper. I would also like to thank Dr. B. Kustow, whose patient the child is, for his permission to look after the child, and for his encouragement.

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Stuart Carne

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