the same day her haemoglobin dropped to 5.4 g. with 5% reticulo-
cytes. A second blood transfusion was given, steroids were continued, and chloramphenicol was started. Her temperature dropped within three days and she remained afebrile. The haemoglobin was 8.5 g. on the twenty-seventh day of the illness and 10.5 g. a month later.

**Comment**

All five cases were anaemic on admission, the haemoglobin ranging from 9.8 to 6.4 g. In three there was a further drop in haemoglobin after starting treatment with chloramphenicol, but in two (Cases 2 and 5) there was a marked drop in haemoglobin before the children had received any drug therapy whatso-
ever. We would like to stress that none of the children received antipyretics such as aspirin or amidopyrine. Cold sponging was used for reduction of temperature.

The clinical course of the disease was in no way more severe in the children who haemolyzed than in those who did not.

The inherited defect of G-6-PD deficiency may result in haemolysis after the individual is exposed to various drugs, including chloramphenicol. Steinberg et al. (1958) and Brunetti et al. (1959) are of the opinion that infection per se is an exogenous trigger mechanism. Despite the fact that all five of our patients who haemolyzed received chloramphenicol, it is felt that this can be exonerated as the sole cause of the haemol-
ysis, and that in two if not all of our cases it was the infection which acted as a trigger mechanism for the production of haemol-
ysis. All five patients were anaemic on admission, and in Case 2 there was unequivocal evidence of haemolysis before starting treatment with chloramphenicol. Case 5 also showed haemolysis with relapse of the typhoid after a 10-day interval, and before chloramphenicol was restarted. There appears to be a fairly constant time relationship between the natural history of the disease and the appearance of the anaemia, which would support the view that it is the disease process and not the therapy that is the operative factor. This time relationship is true not only in our patients who received chloramphenicol but also in those reported in earlier years who did not receive this drug. We should like to stress, however, that in no way do we consider as specific the action of typhoid as a trigger mechanism for haemolysis in G-6-PD-deficient individuals. Other infec-
tions probably act similarly in enzyme-deficient patients.

G-6-PD deficiency is common in Israel among oriental Jews, who make up a large proportion of the population, and this may well explain why haemolysis as a complication of typhoid fever is well known in Israel (Berman et al., 1945; Winter and Solomon, 1954; Marberg, 1963), whereas in countries where the gene frequency of G-6-PD deficiency is low reports on haemolysis are exceedingly rare. It is felt that it would be worthwhile to confirm the relationship between the frequency of haemolysis in infection and the existence of an erythrocyte enzyme deficiency in other countries where there is a high gene frequency of erythrocyte enzyme deficiency.

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**References**


**Lymphadenopathy and Megaloblastic Anaemia in Patient Receiving Primidone**

**[With Special Plate]**


The rarer complications of anticonvulsant therapy include the megaloblastic anaemias, due to a disturbance of folic acid metabolism, and lymphadenopathies, which clinically and morphologically resemble a reticulosis. Both have followed the administration of hydantoins anticonvulsants, but lymphadenop-
athy has not previously been described in a patient taking primidone (Mysoline), an anticonvulsant which Bogue and Carrington (1953) consider to be a derivative of phenobarbitone.

This communication reports the occurrence of lymphadenopa-
thy, megaloblastic anaemia, and thyroid enlargement in a man who had taken primidone for four years.

**Case History**

The patient, a 71-year-old man, had suffered since 1960 from grand-mal epilepsy due to cerebral artherosclerosis. From 1961 until his admission to hospital the only drug taken for this was primidone (750 mg. daily).

In August 1965 he was referred to hospital because of thyroid enlargement. In addition, enlarged lymph nodes varying from 1 to 3 cm. in size were present on both sides of the neck. No other group of lymph nodes was enlarged nor was there any enlarge-
ment of liver or spleen. He failed to report back to hospital until October, when he did so because of loss of weight (from 89 to 65 kg., height 170 cm.), fatigue, exertional dyspnoea, and an episode of diarrhoea lasting two weeks. He was anaemic (Hb 7.8 g.) and there was an associated leucopenia (W.B.C. 1,500/cu. mm.).

On 7 October a lymph node was removed from the left carotid chain. Because the histological appearances were thought to be consistent with those of Hodgkin’s disease, he was transferred to the department of radiotherapy, Western General Hospital, Edinburgh, for further investigation.

The anaemia was found to be due to folic acid deficiency. Blood count: Hb 8.7 g., P.C.V. 27.0%, M.C.H.C. 32.2%; W.B.C. 2,050/cu. mm.; platelets 80,000–190,000/cu. mm. Peripheral blood film: macrocytosis and anisocytosis; multilobed polymorphs, lymphopenia, and eosinophilia. Sternal marrow (see Table). Serum vitamin B12, serum folate, and serum iron all normal. Figlu ++ +. Free acid was present in fasting gastric juice. Barium meal and follow-through examination negative.

The original lymph-node biopsy (Special Plate, Figs. 1 and 2) was reviewed and reported on as follows: “The normal architecture has been destroyed by the proliferation of abnormal cells, which are probably reticulum cells. There is a marked tendency to individual cell degeneration without any area of necrosis. The better-preserved cells have a rather ill-defined cytoplasm with one or more large and pleomorphic nuclei, usually containing several large nucleoli. Mitotic figures are not infrequent. In the more degenerate cells
the cytoplasm is abundant, granular, eosinophilic, and often vacuolated. There is a considerable admixture of lymphocytes. There is no gross increase in reticulin. In conclusion, this is probably a neoplastic disease affecting the reticulum cells, perhaps the reticulum-cell medullary reticulosis of Robb-Smith (1947)."

Because of the association between other anticonvulsants and a lymphadenopathy resembling a reticulosis, it was decided not to irradiate the enlarged nodes. Primidone was stopped on 3 November, and thereafter phenobarbitone 90 mg., folic acid 10 mg., and ferrous sulphate 600 mg. were given daily.

Fourteen days after stopping primidone there was a further distinct increase in the size of the thyroid gland, lasting for seven days, although clinically the patient was euthyroid. Results of investigation of thyroid function were as follows: protein-bound iodine 3.9 mg./100 ml.; tests for thyroid antibodies strongly positive (microsomal complement fixation test positive 1:512; agar diffusion for thyroglobulin positive; tanned-cell haemagglutination positive 1:25,000); 131I uptake normal; protein-bound 11I normal.

On 10 December an open thyroid biopsy was done. The histological appearances were characteristic of Hashimoto's disease, and the amount of hyalinization in the fibrous septa suggested that the process was of long standing.

At the same time two lymph nodes were removed and were reported on as follows: "The architectural pattern is reasonably well preserved. Follicles are arranged fairly regularly round the cortex, but are less well demarcated than normal. Their cells are hyperchromatic and show a tendency to degeneration and vacuolation. Between the follicles there is a complex mixture of plasma cells, lymphocytes, a few eosinophils, and quite numerous abnormal reticulum cells with prominent nucleioli. Most of the reticulum cells have abundant eosinophilic cytoplasm and a number of them have two nuclei, sometimes arranged as a mirror image of each other. The abnormal reaction in this lymph node has persisted for some time after the withdrawal of primidone, but the architecture has reverted towards normality." (Special Plate, Fig. 3).

Within a week of stopping primidone the lymph nodes were smaller; two weeks later they were not palpable, and have remained so. The response to folic acid and iron is shown in the Chart, and the changes in three marrow aspirations are summarized in the Table.

The patient was discharged from hospital on 18 December, has gained weight, and returned to normal activity. The thyroid gland remained slightly enlarged (17 August 1966).

LYMPH NODES

Saltzstein and Ackerman (1959) reviewed 82 cases in which lymphadenopathy occurred after the administration of a hydantoin anticonvulsant. They emphasized the following points. The cervical nodes are usually involved, they are often tender, and the lymphadenopathy is commonly associated with other signs of drug sensitivity such as eosinophilia, fever, blood dyscrasias, and skin eruptions. The lymphadenopathy may become obvious one week after the beginning of medication. In only three cases was the latent period longer than four months.

In our case the enlarged nodes were cervical but were never painful or tender. Clinically the nodes, which were firm, discrete, and mobile, were quite compatible with a diagnosis of Hodgkin's disease. The patient had had no skin eruptions, and his temperature was normal throughout his stay in hospital.

If it is assumed that the lymphadenopathy occurred at the same time as the thyroid enlargement, then the latent period is about four years. This is in marked contrast to the findings of Saltzstein and Ackerman.

Saltzstein and Ackerman emphasized the obliteration of the normal lymph-node architecture, the cellular pleomorphism, and the hyperplasia and abnormality of the reticulum cells. All these features conform to the description of the histology from the first node biopsy in our case. It is of some importance that, although the normal pattern of the lymph node was completely obscured in sections stained by haematoxylin and eosin, the reticulin pattern showed little disturbance. In fact, preservation of the reticulin architecture may be of value in distinguishing between an abnormal reactive hyperplasia and neoplasia. When the reticulin pattern is relatively normal the possibility of a drug reaction should be excluded in all cases of unusual lymph-node histology before the administration of radiotherapeutic or cytotoxic drugs. This is particularly advisable when, as in the present case, the histology resembles that of the reticulum-cell medullary reticulosis, described by Robb-Smith (1938) as a rare form, in adults, of Letterer-Siwe disease, in which lymphadenopathy, statorrhoea, and macrocytic anaemia responsive to folic acid may occur (Robb-Smith, 1947; Taylor, 1956).

BLOOD CHANGES

Anaemia due to a disturbance of folic acid metabolism has occasionally been reported after the administration of various hydantoin derivatives, barbiturates, or primidone (Badenoch, 1954; Fulh and Moorhouse, 1956; Hawkins and Meynell, 1958; Chanarin, Laidlaw, Loughridge, and Mollin, 1960). Macrocytosis, in the absence of overt anaemia, has been reported in epileptics receiving anticonvulsants (Hawkins and Meynell, 1958).

In our case the megaloblastic anaemia was associated with leucopenia, thrombocytopenia, and eosinophilia (800 eosinophils per cu. mm.) in the peripheral blood. The marrow showed a marked depression of granulopoiesis. Half the granulocyte

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**Table: Sequential Marrow Changes**

<table>
<thead>
<tr>
<th>Date</th>
<th>Appearance</th>
<th>M/E Ratio</th>
<th>% Retic. Cells</th>
<th>% Neutrophil Myelocytes</th>
<th>% Eosinophil Myelocytes</th>
<th>% Neutrophil Metamyelocytes</th>
<th>% Eosinophil Metamyelocytes</th>
<th>Lymphocytes</th>
<th>Megakaryocytes</th>
<th>Plasma Cells</th>
<th>Promyelocytes</th>
<th>Myeloblasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 Oct. Diagnostic</td>
<td>Megaloblastic normoblastic</td>
<td>0.2:1</td>
<td>1.5</td>
<td>3.5</td>
<td>2.0</td>
<td>16.5</td>
<td>5.0</td>
<td>7.0</td>
<td>0.5</td>
<td>8.5</td>
<td>0.5</td>
<td>48</td>
</tr>
<tr>
<td>24 Nov. 3 weeks after stopping primidone</td>
<td>Megaloblastic normoblastic</td>
<td>0.4:1</td>
<td>1.5</td>
<td>11.5</td>
<td>2.5</td>
<td>14.5</td>
<td>3.5</td>
<td>0.5</td>
<td>0.5</td>
<td>3.5</td>
<td>1.5</td>
<td>51</td>
</tr>
<tr>
<td>24 Jan. 12 weeks after stopping primidone</td>
<td>Megaloblastic normoblastic</td>
<td>1:1</td>
<td>0.5</td>
<td>15.5</td>
<td>2.5</td>
<td>22.5</td>
<td>5.0</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>1.5</td>
<td>30</td>
</tr>
</tbody>
</table>

* Includes band forms and segmented cells.

Note: The table does not include the percentages of all cells present in the marrow.
precursors in the marrow were of the eosinophil series. Several of the cases reviewed by Saltzstein and Ackerman were recorded as having anaemia, aplastic anaemia, or pancytopenia, but in none was it suggested that the anaemia was due to a disturbance of folic acid metabolism.

A long latent period between the start of treatment and the development of anaemia in certain cases has led some authors to postulate that there may be additional precipitating factors such as dietary deficiency or the increased physiological demands of pregnancy (Gydell, 1957; Horsfield and Chalmers, 1963; Reynolds, Hallpike, Phillips, and Matthews, 1965; Gatenby, 1960). It is possible that dietary factors contributed to the development of the anaemia in our patient. When he sought advice for the second time he admitted to dieting, but complained of marked loss of weight and diarrhoea in addition to symptoms attributable to his anaemia. In retrospect the loss of weight appears excessive, and may have been caused by impaired intestinal function.

Thyroid

The goitre which developed in our patient is of some interest because it has been suggested that hydantoin anticonvulsants may have an effect upon thyroid metabolism by inhibiting binding between thyroxine and serum $\alpha$-globulin (Oppenheimer and Tavernetti, 1962). This results in low values of serum protein-bound iodine, but is not reflected in other measures of thyroid function or in clinical hypothyroidism. Thyroid-function tests, including protein-bound iodine, were normal in our patient.

Bogue and Carrington (1953) reported morphological changes in the thyroid gland in over 50% of rats exposed to large doses of primidone. The histological findings in the thyroid biopsy five weeks after the withdrawal of primidone were not suggestive of the changes described by Bogue and Carrington. Our patient had Hashimoto's disease, and we feel that the sudden and labile enlargement of the thyroid gland coinciding with the lymphadenopathy may have been due to a reaction in its lymphoid components similar to that which occurred in the cervical nodes. It must be noted, however, that the discontinuation of primidone was followed by a further transient thyroid enlargement. If primidone has a hyperplastic effect upon thyroid epithelium, as Bogue and Carrington suggest, then any involution of thyroid epithelium after stopping the drug may have exacerbated the autoimmune reaction and caused a transient enlargement of lymphadenoid type.

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REMARKS


Massive Pulmonary Embolism

[WITH SPECIAL PLATE]


The ability to maintain the circulation by cardiopulmonary bypass while exploring the pulmonary arteries has made the operation of pulmonary embolectomy feasible. Given the requisites of rapid accurate diagnosis and facilities for cardiopulmonary bypass an increasing number of otherwise fatal cases of massive pulmonary embolism will be salvaged. The following case is of interest in that massive pulmonary embolism led to cardiac arrest in an apparently fit young nurse without any evidence of, or cause for, venous thrombosis. Acute enlargement of the pulmonary arteries suggested the correct diagnosis. Pulmonary embolectomy was successfully performed, and illustrated the necessity for manually massaging the lungs at operation for successful removal of all clot.

Case History

A 21-year-old nurse developed sudden pleuritic pain in her right lower chest. Apart from the pain she felt well and continued with her ward work. After the pain had persisted for three days she presented herself for medical examination on 10 December 1964. Examination at the time showed a temperature of 99.5°F (37.6°C) and slight tachypnoea, but no other abnormality. Investigations showed: haemoglobin, 12.5 g./100 ml; white-cell count, 9,700/c.mm., with a normal distribution; E.S.R. 19 mm. Westergren; chest radiography, slight elevation of the right diaphragm (Fig. 1). A tentative diagnosis was made of pleurisy of unknown cause. There was no evidence of thrombophlebitis, nor any history of local injury, medication, or gynaecological disturbances to suggest the occurrence of pulmonary embolism. Over the next two days the patient's pain disappeared and she felt normal.

On the night of 12 December, while returning from opening her bowels, she collapsed with severe central chest pain and dyspnoea. On examination she was pale and sweating, with constricted peripheral veins. There was intense hyperventilation with central cyanosis. The pulse rate was 160, systolic blood-pressure 80 mm. Hg, and the jugular venous pressure raised above the ears. Heart sounds were inaudible because of the uncontrollable hyperventilation. The liver was slightly enlarged and tender. There was no evidence of thrombophlebitis. An electrocardiogram showed right axis deviation and inverted T waves in leads II, III, and AVF. A second chest film (Fig. 2) compared with that taken two days earlier (Fig. 1) showed considerable enlargement of the heart, and particularly the major pulmonary arteries. The transverse diameter of the right descending pulmonary artery, which earlier had
J. A. ARMSTRONG AND MARGUERITE S. PEREIRA: IDENTIFICATION OF "RYAN VIRUS"

FIG. 1.-48-hour-inoculated HeLa-cell culture, showing the appearance of amoebae (one of which is arrowed) at moderate magnification. (x550.)

FIG. 2.-High-power microscopical view of two hartmannellid amoebae as seen in an inoculated human-embryo-kidney-cell culture, showing the characteristic nuclear morphology and cytoplasmic vacuolation. (x1,560.)

A. O. LANGLANDS ET AL.: LYMPHADENOPATHY IN PATIENT RECEIVING PRIMIDONE

FIG. 1.—Lymph node 7 October 1965, showing loss of normal architecture due to infiltration by abnormal reticulum cells. (x69.)

FIG. 2.—Lymph node 7 October 1965, showing infiltration by abnormal and sometimes vacuolated reticulum cells. (x345.)

FIG. 3.—Lymph node 10 December 1965 (five weeks after stopping primidone), showing partial return of follicular structure and decrease in number of abnormal reticulum cells. (x69.)