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after-effects in later life. The investigations are being continued and it is proposed in the near future to send sections to the London School of Tropical Medicine.

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REFERENCES

CLINICAL RECORDS
A FATAL CASE OF PURPURA HAEMORRHAGICA WITH AGRANULOCYTIC ANGINA AFTER ARSPHENAMINE THERAPY

The occurrence of blood dyscrasias after antisypililitic treatment with compounds of the arsphenamine group is an uncommon complication but one which is often of grave import. These dyscrasias are usually classified into three main types: (1) thrombocytopenic purpura, (2) granulocytopenia, and (3) aplastic anaemia. Although the literature on this subject is far from voluminous, reports of instances of each of these main types are readily found. Occasional reports suggest that cases cannot always be readily classified in any one of these three groups.

The following case, which showed the characteristics of both type 1 and type 2, exhibited marked purpuric haemorrhages, together with the rare complication of haematuria, and granulocytopenia with severe faucial ulceration, which proved fatal, also developed.

Case report
On December 3rd 1940 a married woman, aged 27 years, was transferred to this clinic bearing documents (Booklet V15) which indicated that she had commenced treatment for secondary syphilis and had received, one week earlier, 0·06 gramme of mapharsen and 0·4 gramme of bismuth. Her general condition was good, with weight 7 st. 13 lb. A fading rash was still perceptible. The heart was normal. The urine did not contain any albumin.

During the period from 3rd December 1940 to 11th February 1941 she received a total of 4 grammes of stabilarsan (arsphenamine and glucose) and 1·4 grammes of bismuth. She showed no sign of intolerance and made a slight gain in weight. On 18th February potassium iodide was prescribed, but to this drug intolerance was shown by the occurrence of a rash and of swollen glands. These signs quickly disappeared when the drug was omitted. She was given 0·45 gramme of stabilarsan on 14th March and on her next attendance on 25th March a papular rash was evident on her back and legs. She was therefore treated with six injections of 0·6 gramme of calciosalt (calcium thiosulphate) during the next fourteen days, and by 15th April the rash had disappeared and she appeared to be well. The blood Wassermann reaction, which had been strongly positive on her first attendance, was still strongly positive on this date.

When she attended on 22nd April she was found to have slight oedema of both feet. The urine contained a few pus cells and a trace of albumin but renal casts were absent. The heart appeared to be normal and there were no obvious varicose veins. The oedema had disappeared by 13th May. On 10th June the blood Wassermann reaction was found to be negative.

In view of these signs of intolerance and of the negative Wassermann reaction at this time, she was kept under surveillance up to March 1942, when she was found to be 6 months pregnant. The Wassermann reaction was still negative but, on account of the pregnancy treatment with 3 grammes of quinostab (quinine iodobismuthate suspended in olive oil) was given from 24th March to 6th May. A healthy child was born on 25th June.

On 3rd August the Wassermann gave a doubtful result, but this was positive on 28th August after a provocative injection of 0·3 gramme of neoarsphenamine. She made no further attendance until October, when the provocative Wassermann result was again positive. There were no signs of clinical relapse. She had an illness which was reported as " influenza ". Shortly afterwards and was away from the clinic until 4th January 1944. On this occasion treatment with potassium iodide was well tolerated. On 10th February, as the blood
CLINICAL RECORDS

Wassermann and Kahn tests were returned as strongly positive, she was treated with 0·2 grammes of bismuth, to which was added on 15th February 0·3 grammes of stabilarsan. Treatment with stabilarsan, 0·45 grammes and bismuth, 0·2 grammes was given at weekly intervals until 30th March, when a deposit of bismuth ("bismuth line") was noticed on the gum margin, but all other signs of treatment intolerance were absent. The antisyphilitic therapy was discontinued and oral hygiene arranged with a dental surgeon.

This patient was not seen again until a week later (7th April) when she was immediately admitted into hospital. The medical history was as follows. On 31st March, the day after her last attendance at the clinic, she noticed swellings under both sides of the lower jaw; the gums and throat became painful. Next day the gums began to bleed and clots formed at the gum margin. During the next three days she noticed dark spots on the left elbow, left leg and neck. On 4th April her left arm felt numb and the vision of the left eye became dim. Three days later the urine was noted to be of a dark colour and the stool was tarry.

### TABLE 1.—DIFFERENTIAL AND TOTAL WHITE CELL COUNTS

<table>
<thead>
<tr>
<th>LEUCOCYTES</th>
<th>10th April</th>
<th>11th April</th>
<th>12th April</th>
<th>13th April</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total white cells per cubic millimetre</td>
<td>500</td>
<td>600</td>
<td>800</td>
<td>700</td>
</tr>
</tbody>
</table>

#### Percentages of

| Polynuclear cells | 20 | 8 | 5 | 4 |
| Lymphocytes | 72 | 88 | 91 | 92 |
| Large mononuclear cells | 4 | 3 | 4 | 4 |
| Eosinophil cells | 4 | 1 | — | — |

On admission to hospital the woman looked ill; her temperature was 102·8°F., pulse 132, respiration 20. The gums were swollen and blood-stained, there was a necrotic ulcer on the right side of the soft palate and the tongue was brown and coated. Purpuric spots were present on the front of the neck, the left arm, the right side of the chest, the left thigh and the back. Cardiac examination revealed a systolic murmur at the apex and base. The spleen could not be felt. The bleeding time was more than ten minutes.

One pint of stored whole blood was given—the patient was classified Group A—and the following treatment instituted: ascorbic acid, 500 milligrammes orally twice daily; thistab (sodium thiosulphate), 0·9 grammes intravenously once daily; pentide (sodium pentose nucleotide), 10 cubic centimetres intramuscularly once daily. On the following day a second pint of stored whole blood was given, also 2 cubic centimetres of hemoplastin (prothrombin and antithrombin) for the continued bleeding from the gums.

Pathological investigations, not available until 10th April, revealed the following results. White blood cell count was only 500 per cubic millimetre: polymorphonuclears, 20 per cent; lymphocytes, 72 per cent; large mononuclears, 4 per cent; eosinophils, 4 per cent. Throat swab: direct film showed a few Vincent’s spirochaetes and fusiform bacilli. Culture showed a few colonies of haemolytic streptococci. On the same day (10th April) one pint of fresh blood was transfused with good response. The pentide administration was increased to 10 cubic centimetres twice a day. The ascorbic acid was reduced to 100 milligrammes twice a day, the patient having had a total of 2·5 grammes.

Next day (11th April) a blood count showed haemoglobin to be 42 per cent; the red corpuscles were 2,080,000 per cubic millimetre; the colour index was 1·0. The total white cell count—600 per cubic millimetre—had very slightly increased but the polymorphonuclear cells were decreasing in number: polymorphonuclears, 8 per cent; lymphocytes, 88 per cent; large mononuclears, 3 per cent; eosinophils, 1 per cent. The blood platelets numbered only 17,000 per cubic millimetre. In view of the fact that the patient had had three pints of blood transfused during the previous three days, this result suggested an aplasia of all elements of the bone marrow.

During the following two days the white cell count showed a slight increase, but the ratio of polymorphonuclear cells to the lymphocytes gradually decreased (see Table 1) and fell to a ratio of 4 to 92 on the second day; on this day the platelets numbered only 15,000 per cubic millimetre.

The administration of pentide was increased to 10 cubic centimetres three times a day. The effect of the fresh blood had now ceased, there being again frank haemorrhage from the gums. It was intended to give a further two pints of fresh blood, but the patient died in the evening.

Throughout the course of the illness there was pyrexia of the continuous type, varying from 100°F. to 104·2°F. The pulse varied between 110 and 140 per minute and the respirations between 20 and 30 per minute.

It is of some interest to note that this woman had had two children. The elder died at the age of sixteen months and the cause of death was given as primary...
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anaemia. The younger child died at the age of three months from myeloid leukaemia, but further particulars could not be obtained.

A post-mortem examination was performed by Dr. S. T. Crowther, to whom we are indebted for the following report.

Post-mortem report

There was extensive necrosis of the gums, tonsils and pharyngeal tissues. There were numerous punctate haemorrhages throughout the brain substance. The heart showed no abnormalities. The right lung was adherent to the chest wall and showed evidence of a healed tuberculosis lesion at the apex. Both lungs had large infarcted areas at the bases. The liver was considerably enlarged, was greyish to the touch and appeared pale and fatty. The spleen was much enlarged and contained numerous small infarcts. Both kidneys showed some degree of cloudy swelling, but otherwise appeared normal. The mucous membrane of the stomach was swollen and there were many small haemorrhages in it. Small haemorrhages were also present in the mucous membrane of the small intestine throughout its length. The mesenteric glands were enlarged.

There was a bruise on each thigh and in the region of both shoulders. The arms, legs and abdominal wall were covered with minute petechial haemorrhages.

Microscopical examination

Liver.—All the cells of the liver were turbid and cloudy and showed accumulation of fat. The nuclei stained badly and were ill defined. These changes were very much more marked around the efferent vein than around the portal vein.

Bone marrow.—This showed an almost complete absence of myelocytes. Erythroblasts were present in normal numbers.

Kidneys.—The epithelium of the renal tubules was swollen. The nuclei of the epithelial cells were degenerate and in many cells had disappeared completely. Many of the tubules contained casts and a few contained red blood cells.

Stomach.—The superficial layer of the gastric mucosa was necrotic.

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ANNOTATION

THE JARISCH-HERXHEIMER REACTION

The occasional occurrence of an intensification of the symptoms and signs of syphilis soon after the commencement of specific treatment was commented upon by Jarisch as long ago as 1895. This effect was more fully described in 1902 by Herxheimer, who reported an increase of general constitutional disturbance, such as fever and malaise, in addition to the aggravation of the superficial lesions of the secondary stage, some few hours after the first injection or injection of a mercurial compound. Attention was drawn to the more frequent occurrence of the same syndrome after the initial injection of salvarsan by Finger in 1902, since when the phenomenon has become widely known and usually termed the Jarisch-Herxheimer reaction. The universal use of the arsphenamines, not only in early syphilis but also for the lesions of the later stages of this infection, has given rise to many reports in the medical literature of untoward manifestations, which have been classified as Jarisch-Herxheimer reactions, ensuing shortly after an injection of one of the arsphenamines in various tertiary syphilitic conditions.

Although much controversy has taken place about the exact cause of this effect of treatment, its nature and significance remain obscure. The reaction has been thought to be due to a sublethal and irritative action of the drug resulting in a stimulation of spirochaetal activity, as a result of which these organisms undergo a considerable increase in their number and virulence. On the other hand it has been said by some authors to be the result of a sudden production and release of a large amount of toxic substances, caused by mass destruction and dissolution of spirochaetes by the arsphenamine compound. Because of the scarcity of histological reports, little is known of the pathological changes that take place in the lesions which are affected by the Jarisch-Herxheimer reaction. According to Kolmer there is an increase in intensity of the inflammatory changes, including hyperaemia, serious exudation and infiltration of the tissues with lymphocytes and plasma cells.