must not be allowed to give rise to a false sense of security, and every possible care should be taken in handling material containing it.

Summary

Methods used for the production of human plasma and serum on a large scale are described.

Plasma is separated either by an Alfa-Laval separator or by suction after the cells have settled. It is then pooled in 10-litre bottles for convenience in handling.

Serum is separated by various methods at the blood supply depots and is sent to us in bulk for filtration and bottling.

The plasma and serum are clarified by passage through sterile paper pulp and are then sterilized by Seitz filtration.

Technical details are given of the methods employed to prevent contamination during the various stages of preparation and to ensure sterility of the final products.

Methods similar to the above have been used in and described from various laboratories. In the early days of the work information was freely exchanged between Dr. R. I. N. Greaves, Dr. W. S. Stanbury, Colonel L. E. H. Whitby, and ourselves, and it is impossible always to establish where particular processes originated. Bushby and Whitby (1941) have published an account of a similar procedure, but it was thought that a description of our methods might be of interest.

Our thanks are due to Dr. C. G. Anderson and Mr. J. G. C. Campbell for their helpful suggestions and criticism.

REFERENCES

- Bushby, S. R. M., Buttle, G. A. H., and Whitby, L. E. H. (1940). *Lancet*, 2, 131.
— and Whitby, L. E. H. (1941). *J. R.A.M.C.*, 76, 4.
Della Vida, B. L., and Dyke, S. C. (1941). *Lancet*, 1, 564.
Jakobowicz, R., and Bryce, L. M. (1941). *Med. J. Austral.*, 1, 318.
Loutit, J. F. (1941). *British Medical Journal*, 1, 729.
MacKay, M. E. (1941). *Ibid.*, 1, 747.

THROMBOCYTOPENIC PURPURA COMPLICATING ARSENOBENZENE THERAPY

BY

SYDNEY M. LAIRD, M.D., B.Sc., F.R.F.P.S.G., D.P.H.
Major, R.A.M.C.

Blood dyscrasia complicating arsenobenzene therapy, may, according to McCarthy and Wilson (1932), belong to one of three groups—the thrombocytopenic, the granulocytopenic, and the aplastic. While borderline cases do occur, haematological examination usually permits the placing of any particular patient with symptoms of blood dyscrasia in one of these three categories. Such classification is not merely of academic interest, but points the way to correct treatment and sound prognosis. This paper, in addition to recording another case of arsenical thrombocytopenic purpura, seeks to assess the present-day position of this serious complication of antisyphilitic treatment.

Case Report

The patient, a well-developed man aged 30, started anti-specific treatment on April 9, 1940, at which time he presented clinical evidence of early secondary syphilis, the Wassermann reaction and Kahn test being positive. The first course of treatment was irregular, and by July 25 he had received only three intravenous injections of neoarsenobenzene, five intramuscular injections of sulpharsenobenzene (total 5.4 grammes), and four injections of a bismuth preparation. The second course was started on November 13, at which time the Wassermann reaction and Kahn test were still positive. During this course he received six weekly injections of sulpharsenobenzene intramuscularly (3.45 grammes) and 1.4 grammes of bismuth, the last injection being administered on December 27. On reporting at the clinic on January 1, 1941, for treatment, purpura was noted, and on the following day he was admitted to hospital under my care.

On admission ecchymosis was widespread over the trunk and limbs, being most pronounced on the flexor aspects of the extremities and over the hip-joint areas. The purpuric patches varied from petechiae to large areas of ecchymosis, and there

was a subconjunctival haemorrhage affecting the left eye. Blood was oozing profusely from the gums around all the teeth, and this may have accounted for the marked melaena noted in the stool on the following day. Gross haematuria was present, but there was no evidence of haemorrhages into joints or pleural cavities, nor enlargement of liver, spleen, or superficial glands. The temperature, pulse, and respirations were within normal limits. Apart from discomfort and inconvenience from the bleeding gums, the patient had no subjective complaint and felt well.

Treatment comprised rest in bed, a milk diet, abundant fluids, the juice of two oranges daily, and a mouth-wash of liq. ferri perchlor. every three hours. In addition, 6 c.cm. of 10% calcium thiosulphate solution was given intravenously on admission and repeated the following day. On January 4 the patient's condition remained unchanged, and 1,000 mg. of ascorbic acid was administered by the intravenous route. The next day the clinical condition was still unchanged, and daily injections of calcium thiosulphate were resumed. On January 6 improvement began, the haematuria and bleeding from the gums being noticeably less. It was obvious on the 7th that the purpuric manifestations were abating rapidly, and on the 8th the bleeding from the gums and the melaena had ceased. There was no haematuria on naked-eye examination. From this time no further treatment was given, and convalescence proceeded rapidly, with early fading of the purpuric areas. The subconjunctival haemorrhage remained stationary for a considerable time, but eventually cleared up completely. The results of various examinations of the blood are shown in the table.

Table showing the Results of Blood Examinations

	3/1/41	7/1/41	13/1/41	23/1/41	28/1/41
Haemoglobin ..	102%	88%	89%	96%	—
R.B.C. (millions) ..	5.18	4.17	4.33	4.19	4.85
W.B.C. ..	9,200	5,200	6,100	5,700	—
Platelets ¹ ..	30,00	41,000	70,000	157,000	274,000
Bleeding time ² ..	+ 15 min.	—	9.5 min.	3.5 min.	—
Clotting time ³ ..	3 min.	—	3 min.	—	—
Clot retraction at 24 hours ..	Almost absent	—	Normal	—	—
Capillary fragility ⁴ ..	absent	—	30	—	8

¹ Estimated by the method of Evans (1928).

² Estimated by Duke's method.

³ Estimated by the method of Lee and White.

⁴ Expressed as the number of petechiae per unit area, at standard pressure and time.

Discussion

Aetiology.—The aetiology of the blood dyscrasias following arsenobenzene therapy is not yet clearly understood. In the granulocytopenic and aplastic groups impairment of bone-marrow function is obvious, but the actual mechanism responsible remains in doubt. All the arsenical preparations used in the treatment of syphilis contain a benzene radical, and the action of the latter in causing depression of the bone-marrow function is readily seen in chronic benzene poisoning. The prevailing view, which incriminates the benzene group, is supported by this analogy, but experimental evidence (Lancellotti, 1938; Montanaro, 1938) is inconclusive, and suggests that, although the arsenobenzenes can produce a small transitory depression of the haemopoietic tissues in animals, other factors, such as idiosyncrasy or sensitization, are necessary to bring about the agranulocytic or aplastic complications of antisyphilitic treatment in the human being. Wheelihan (1928) has reported granulocytopenia in a child after treatment with an inorganic arsenical preparation (potassium arsenite), but in this case infection may have played an important part in producing the depression of bone-marrow function.

Purpura develops only after a considerable number of injections, which in many cases have been received at irregular intervals, and this has led to the view that some sensitization mechanism produces the increased capillary fragility. The influence of sensitization is well illustrated in the cases described by Falconer, Epstein, and Mills (1940), who administered very small doses of arseno-

benzene derivatives to patients who had previously shown signs of intolerance to these drugs. Purpuric manifestations resulted; the platelets decreased and then reappeared rapidly. This thrombocytopenic process was entirely uninfluenced by previous saturation of the patients' tissues with ascorbic acid. In contrast, Mu (1929), in a study of the immediate effect of neoarsenobenzene on the platelets of healthy people who had never previously received such a drug, failed to produce purpuric manifestations, although there was some depression of the platelet count. More recently, Scarborough and Stewart (1938) and Horne and Scarborough (1940) have demonstrated that the increased capillary fragility present in arsenical dermatitis and thrombocytopenic purpura is counteracted by treatment with vitamin P, but remains uninfluenced by ascorbic acid.

Incidence.—In 1940 Gorrie, in reporting a case of arsenical purpura haemorrhagica, stated that he had found 21 cases recorded in the literature since McCarthy and Wilson (1932) collected 79 cases and added 2 of their own. Blood dyscrasia following arsenobenzene treatment is probably more common than these figures suggest, as a proportion of cases may remain unrecorded, while in other cases of purpura the relation to arsenical therapy may be missed. A more accurate indication can be obtained from the figures of the Whitechapel Clinic, London. Burke (1940) states that out of 3,250 cases receiving treatment for syphilis at this clinic between 1934 and 1938, 13 (0.4%) cases of blood dyscrasia were noted, 10 of which were of the thrombocytopenic type. Cole *et al.* (1931) observed only 2 cases of purpura haemorrhagica among 1,212 patients treated with various arsenical preparations over a ten-year period.

Symptomatology.—The clinical picture varies with the severity of the thrombocytopenia. Mild cases may show only a few small petechiae in the skin and buccal mucous membrane; other cases may present more definite purpuric manifestations, as illustrated by the case reported above. Haematuria occurs only in the presence of severe thrombocytopenia. No mention of it is made in any of the 13 cases described in the reports of Burke (1940), Winter (1940), and McCarthy and Wilson (1932), but it was present in the case recorded by Gorrie (1940). Retinal haemorrhage is very rare, but has been recorded by Gorrie (1940), Scarf (1934), and Stigaard (1937). In the latter's case cerebral haemorrhage also occurred.

Prognosis.—The importance of determining the type of purpura in any particular patient is reflected in the varying prognoses of the different groups. The mortality rate in the aplastic group is high; 28 of the 34 cases reported by McCarthy and Wilson were fatal. In the granulocytopenic group reported by the same authors, 4 out of 12 died. It is evident, therefore, that the presence of depression of the bone-marrow function calls for a grave prognosis. In contrast the outlook in the thrombocytopenic group seems to be invariably favourable. McCarthy and Wilson (1932) tabulated 12 cases of this group, all of which recovered, and 13 other non-fatal cases have since been recorded. The manifestations of severe thrombocytopenic purpura may be so alarming that it is reassuring to know that the prognosis in such cases is uniformly favourable.

Treatment.—The elimination of residual arsenic from the body is a principle of treatment common to all three groups of blood dyscrasia. In addition to general measures for increasing the rate of elimination, clinical experience suggests that the intravenous use of calcium thiosulphate is beneficial, although Muir, Stenhouse, and Becker (1940) failed to find experimental evidence in animals to support this contention. Repeated blood transfusions and pentose

nucleotide therapy may maintain life in the granulocytopenic and aplastic cases until the bone marrow recovers its haemopoietic function. Recent work (Scarborough and Stewart, 1938; Horne and Scarborough, 1940; Zacho, 1939; Todhunter *et al.*, 1940; Bell *et al.*, 1940; Scarborough, 1940) indicates that vitamin P is more concerned than ascorbic acid in maintaining normal capillary resistance, and treatment with vitamin P preparations may be regarded as almost specific for cases of arsenical purpura. During convalescence, anaemia resulting from the purpuric bleeding will require to be counteracted with iron therapy; in severe cases this object may be achieved more rapidly by blood transfusion.

The further antispecific treatment of cases following upon the occurrence of blood dyscrasia must be cautiously planned, and opinion hitherto has been unanimous in ruling out the further administration of arsenobenzene compounds. Goldberg (1939) reported the successful substitution of mapharsen in the antispecific treatment of a pregnant woman in whom previous therapy with neoarsenobenzene had produced agranulocytic angina. However, much more evidence will be necessary before such a course is likely to be generally adopted.

Summary

The three main types of blood dyscrasia which may complicate arsenobenzene therapy are mentioned, and the importance of this classification in relation to treatment and prognosis is emphasized.

A severe example of the thrombocytopenic type is reported, and the aetiology, incidence, symptomatology, treatment, and prognosis of this condition are discussed with reference to the available literature.

I am indebted to the officer commanding a military hospital for permission to publish this case, and to the D.A.D.P. for the laboratory investigations.

REFERENCES

- Bell, G. H., Lazarus, S., and Munro, H. N. (1940). *Lancet*, 2, 155.
 Burke, E. T. (1940). *British Medical Journal*, 2, 27.
 Cole, H. N., *et al.* (1931). *J. Amer. med. Ass.*, 97, 897.
 Evans, W. H. (1928). *J. Path. Bact.*, 31, 815.
 Fakher, E. H., Epstein, N. N., and Mills, E. S. (1940). *Arch. intern. Med.*, 68, 319.
 Goldberg, M. (1939). *Amer. J. Syph.*, 23, 79.
 Gorrie, D. R. (1940). *Lancet*, 1, 1005.
 Horne, G., and Scarborough, H. (1940). *Ibid.*, 2, 66.
 Lancellotti, M. (1938). *Policlinico (Sez. Med.)*, 45, 573.
 McCarthy, F. P., and Wilson, R., jun. (1932). *J. Amer. med. Ass.*, 99, 1557.
 Montanaro, E. (1938). *Policlinico (Sez. Med.)*, 45, 553.
 Mu, J. W. (1929). *Proc. Soc. exp. Biol., N.Y.*, 28, 407.
 Muir, K. B., Stenhouse, E., and Becker, S. W. (1940). *Arch. Derm. Syph.*, Chicago, 41, 308.
 Scarborough, H. (1940). *Lancet*, 2, 644.
 and Stewart, C. P. (1938). *Ibid.*, 2, 610.
 Scarf, M. (1934). *J. Amer. med. Ass.*, 102, 2159.
 Stigaard, A. (1937). *Ugeskr. Laeg.*, 99, 138.
 Todhunter, E. N., Robbins, R. C., Ivey, G., and Brewer, W. (1940). *J. Nutrit.*, 19, 113.
 Wheelahan, R. Y. (1928). *Amer. J. Dis. Child.*, 35, 1032.
 Winter, H. G. (1940). *J. R.A.M.C.*, 74, 161.
 Zacho, C. E. (1939). *Acta path. microbiol. scand.*, 18, 144.

The following are among the recently elected Fellows of the Royal Society of Edinburgh: Satish Chandra Das, M.B., lecturer in pharmacology, Robertson Medical School, Nagpur, C.P., India; Andrew Davidson, M.D., D.P.H., Chief Medical Officer, Department of Health for Scotland; George Henry Edington, D.Sc., M.D., F.R.C.S.; Daniel Lamont, M.B., F.R.C.S.Ed., surgeon, Glasgow Royal Cancer Hospital and Glasgow and West of Scotland Radium Institute, and assistant surgeon, Glasgow Royal Infirmary; Walter Michel Levinthal, M.D., bacteriologist to the Royal College of Physicians Laboratory, Edinburgh; James Macfarlane, M.B., D.P.H., Medical Liaison Officer, Scottish Office, London; Jocelyn Patterson, M.Sc., Ph.D., lecturer in biochemistry at Charing Cross Hospital Medical School; William John Brownlow Riddell, M.D., D.O.M.S., Tennent Professor of Ophthalmology, University of Glasgow; John Douglas Robertson, D.Sc., M.D., D.P.H., Courtauld Institute of Biochemistry, Middlesex Hospital; Joseph G. Tait, M.R.C.S., L.R.C.P., D.P.H., resident secretary in Scotland of the Pharmaceutical Society.