V

BLOOD-DYSCRASIA

IN THE TREATMENT OF VENEREAL DISEASES *

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DEFINITIONS

Moore (1933) classifies the post-arsphenamine blood-dyscrasias into four groups: (a) *Thrombocytopenia*—Purpura hæmorrhagica belongs to this class. In all other purpuras the platelets are normal; (b) *Granulocytopenia* (Agranulocytic angina)—where there is a great decrease in the number of polymorphonuclear neutrophils and eosinophils; (c) *Thrombo-granulocytopenia*—a combination of the two foregoing classes—presenting clinically as an acute purpura hæmorrhagica with a blood-picture showing a diminution of both platelets and granulocytes; and (d) *Aplastic anæmia* where there is great leucopenia with a relative lymphocytosis and a great diminution of platelets. There is also an absence of nucleated erythrocytes and very slight poikilocytosis and anisocytosis.

My opinion is that Moore's classification is needlessly complicated and that it is impossible accurately to make such a differentiation either clinically or hæmatologically between the conditions he enumerates. I suggest that Moore's four classes are but different stages and degrees of the same essential condition and that they merge, the one into the other, in such a way that a sharp distinction between them cannot be made. The essential condition might conveniently be termed "Arsphenamine blood dyscrasia," and it can be divided into two stages: 1. *Thrombocytopenia*—where the only change from the normal in the blood-picture is a decrease in the number of platelets. In pure thrombocytopenia there is a pre-purpuric phase where the decrease of platelets has not progressed far enough to give rise to vascular leakage. One has the impression also, that even with a marked drop

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in platelets hæmorrhages do not occur until some damage has been sustained by the capillary endothelium. In this stage there is no leucopenia and no diminution of neutrophils and eosinophils. For purposes of classification "*mild* thrombocytopenia" means a platelet-count of from 300,000 to 100,000; "*moderate* thrombocytopenia," a count of from 100,000 to 40,000; and "*severe* thrombocytopenia" a count below the critical level of 40,000.

2. *Granulocytopenia*.—This is a development of thrombocytopenia and indicates that the bone-marrow damage is now extending. There are probably two factors involved here: (1) an aplastic process in which there is a more or less complete failure of the marrow to form megaloblasts, Doan's cells or megakaryocytes; and (2) an abundance of these precursor cells may be produced but they may fail to mature—a maturation defect. The latter is probably the predominant factor and this seems to be borne out by the fact that such cases respond to the administration of pentose nucleotide much more satisfactorily than do cases of pure aplastic anæmia. This stage embraces the three groups of Moore—granulocytopenia, thrombo-granulocytopenia and aplastic anæmia. There is a decrease of platelets—except where the etiological agent is sulphonamide—leucopenia, diminution of neutrophils and eosinophils with a relative lymphocytosis. Normoblasts are absent and there is usually only slight poikilocytosis and anisocytosis. The blood-picture is frequently that of typical aplastic anæmia but the bone marrow appearances are more suggestive of "agranulocytosis"—a slight leucoblastic hyperplasia, especially in the upper third of the femur.

Dickson (1935) points out that granulocytopenia is often referred to as "agranulocytosis"—a term proposed by Schultz in 1922; but that term is not a good one since "agranulocyte" was the name originally chosen for those neutrophils devoid of granules which are found in leukæmia. Friedmann used the term "agranulocytic angina" because of the severe throat-lesions which are usually present; but, as Dickson observes, that name is not to be recommended because cases occur in which throat-lesions are absent and also because the term conveys the idea that the infection of the mouth causes the granulocytopenia, whereas the reverse is the case. To grade this condition into "mild," "moderate"

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or "severe," there requires to be taken into consideration not only the hæmatological picture but also the clinical condition.

The chief clinical manifestations of thrombocytopenia and granulocytopenia are the occurrence of subcutaneous hæmorrhage—purpura—and hæmorrhage from mucous membranes.

POST-ARSPHENAMINE BLOOD-DYSCRASIA

ETIOLOGY

There are three elements involved in the natural prevention of hæmorrhage: (1) integrity of the vessel-walls, (2) normality of the blood-coagulation complex, and (3) a sufficient number of blood-platelets.

Syphilis itself, the agents used in its treatment, and some of the drugs administered for gonorrhœa, are all capable of causing serious interference with one or more of these elements. Purpura may follow the administration of amidopyrin, antipyrin, antitoxins, arsenicals, benzoic acid, calx sulphurata, chloral, chloroform, copaiba, cubebs, ergot, hyoscyamus, iodoform, lead acetate, phosphoric acid, potassium chlorate, sandalwood oil, quinine, salicylates, stramonium, sulphonamides, and sulphonal. It has also been recorded as occurring after vaccination for smallpox.

VESSEL-WALLS.—Syphilis is essentially a disease of the peri-vascular lymph-channels; and, while its end-result is to cause an obliterative endarteritis and periarteritis, there occurs during the acute stage of the disease—the secondary phase—cutaneous and mucous-membrane manifestations which are in great part due to an increased permeability of the vessel-walls. Schönlein's purpura resembles secondary syphilis in many respects. It begins with a sore throat, there are arthritic pains and macular cutaneous lesions appear. It would seem, then, that syphilis and *purpura arthritica* possess some common factor which allows vascular leakage.

Peacock (1924) in describing two cases of purpura hæmorrhagica came to the conclusion that the condition was due to destruction of the capillary endothelium allowing the blood to leak through. In both cases the clotting time was normal and this was taken to indicate that there was neither a fall in the number of platelets

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nor any interference with the blood-coagulation complex. Borbély (1930) drew attention to the fact that arsphenamine increased capillary fragility. Horne and Scarborough (1940) showed that in post-arsphenamine erythema and dermatitis there is an associated low capillary resistance.

Emanuel (1933) reported a fatal case of universal purpura with hæmorrhage from mucous-membranes, and he was of the opinion that this was due to injury to the capillary epithelium. Tidy (1926) and Mackay (1931) regard increased permeability and damage to the capillary endothelium as the most important cause of purpura.

BLOOD-COAGULATION COMPLEX.—Both syphilis and the arsphenamines are capable of inflicting damage upon hepatic cells. If this is sufficiently intense, it may seriously interfere with the production of prothrombin. Oliver and Douglas (1923) found that "606" did not act as an anti-thrombin in causing incoagulability, although when it came into contact with that part of the blood-coagulation complex containing fibrinogen, a marked anticoagulating effect was produced. The drug apparently acts directly upon the fibrinogen.

Coagulation is caused by the action of thrombin upon the soluble fibrinogen with the production of the insoluble fibrin. Thrombin is not, of course, present as such in the circulating blood, but in the form of the inactive prothrombin. Activation is brought about by free calcium ions and thrombokinase—the latter being liberated by the disintegration of blood-platelets. The mechanism of coagulation according to the theory of Morawitz is :—

Prothrombin + Calcium ions + Thrombokinase =
Thrombin.

Thrombin + Fibrinogen = Fibrin.

Although hæmorrhage may be due in part to lack of fibrinogen because of liver damage or a destruction of it by arsphenamine, the good results obtained by treatment with calcium suggest that a potent causal factor is a deficiency of calcium in the blood.

Flandin and Tzanck (1921) were apparently the first to call attention to the anticoagulating effect of the arsphenamines upon the blood, both *in vitro* and *in vivo*. They found that if blood is collected in a glass tube the sides of which have been moistened with a weak solution

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of "914," coagulation is delayed for from 30 minutes to 24 hours or longer. If further samples of blood are taken at intervals, incoagulability continues for a period varying from several hours to several days. This phenomenon gradually passes off. They are of the opinion that the anti-coagulating effect is due to the arsphenamine and that it has nothing to do with the syphilis. It occurs in non-syphilitics. According to Flandin and Tzanck the arsphenamine does not seem to act upon the cellular elements of the blood but upon thrombin or its precursors.

Trost (1922) found that "914" is, among organic arsenical compounds, that which is most prone to impede coagulation of the blood *in vitro*.

Anwyl-Davies and Mellanby (1923) reported that an addition of 1 part of arsphenamine to 1,000 parts of blood prevented coagulation *in vitro*. A similar concentration given intravenously to rabbits temporarily (less than an hour) prevents coagulation. After an hour normal coagulability returns. In their experience, therapeutic doses used in human therapy have practically no effect upon coagulation except to a slight degree after prolonged administration. During their *in vitro* experiments they found that blood-coagulation is prevented by adding 0.1 per cent. of arsphenamine to the blood, and that the anticoagulant action is exerted in the last phase of coagulation, *i.e.*, during the interaction between thrombin and fibrinogen. They consider that arsphenamine unites directly with fibrinogen and that the resulting complex is less readily coagulated by thrombin. They found that all the arsphenamine-preparations do not equally affect the coagulability of the blood, thus: neo-arsphenamine and sulpharsphenamine are distinctly effective in preventing coagulation, but Stabilarisan—which is one molecule of arsphenamine base linked to two molecules of glucose—has no such anticoagulant action. Anwyl-Davies and Mellanby consider it probable that the portion of the arsphenamine-base which combines with the glucose is that which, in the absence of glucose, combines with fibrinogen. In this connection they call attention to the finding that inorganic arsenicals do not affect coagulation in any degree. They consider that the combination of arsphenamine with fibrinogen must be due to the particular molecule structure which enables

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combination with glucose to take place as readily as with fibrinogen.

The *in vivo* experiments of Anwyl-Davies and Mellanby were carried out on rabbits. The amount of neo-arsphenamine injected into the animal was equivalent to an injection of 10 grams into the human subject. Before injection, the blood-coagulation time for the rabbit was 2 minutes. Blood withdrawn 10 minutes after injection showed no coagulation in 24 hours, while blood withdrawn 1 hour after injection, coagulated in the normal time of 2 minutes. Contrary to the results obtained by Flandin and Tzanck, Anwyl-Davies and Mellanby report that there was no tendency for arsphenamine to accumulate in the blood and produce cumulative effects. They also found that Stabilarsan did not affect the coagulability of the blood *in vivo* and that the glucose it contains is not detached from the arsphenamine-base before absorption from the blood. In their clinical experiments they found that intravenous injections of therapeutic doses had practically no effect upon the coagulability of human blood. The coagulation-figures for Stabilarsan—which compound does not affect coagulability—did not differ appreciably from those of neo- and sulpharsphenamine, both of which entirely prevent coagulation *in vitro*.

Emile-Weil and Isch-Wall (1923) found that the addition of two drops of human serum to an aqueous solution of sulpharsphenamine caused colloidal precipitation to take place, which precipitate becomes dissolved when more serum is added. If the serum is taken from a purpuric patient, flocculation takes place; but the precipitation is not dissolved on the further addition of serum. These workers believe that post-arsphenamine purpura is of that nature of "colloidoclastic shock" and that it occurs in patients suffering from hepatic insufficiency. Such persons have few or no hæmatoblasts in the blood and they possess an especially fragile capillary system.

Copher (1924) could find no appreciable change in the coagulability of the blood upon the addition of arsphenamine.

It seems that the balance of evidence, experimental and clinical, goes to show that the arsphenamines are capable of so altering the non-cellular elements of blood-coagula-

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tion complex that the tendency to hæmorrhage is increased. It would also appear that into this there enters the matter of individual idiosyncrasy.

BLOOD-PLATELETS.—In 1906, Wright (1906) put forward the theory that the blood-platelets are derived from the megakaryocytes and this has been accepted by the majority of hæmatologists. More recently, however, Hittmair (1938) and also Tocantins (1938) in reviewing this subject have pointed out that the evidence in support of Wright's theory is not completely convincing. A leading article in the *British Medical Journal* for 26th November, 1938, page 1090, states that more plausible theories are (1) that fragmentation of the pseudopods produces platelets in the same way as the mammary epithelium degenerates into colostrum granules, or (2) that the megakaryocytes exert a physico-chemical influence on the neighbouring fluid in the same way as the fibrocytes lay down collagen fibres in the intercellular spaces. Megakaryocytes are present not only in the bone-marrow, but also in the spleen and in the lungs (Howell, 1937). It is therefore quite probable that a great deal of platelet production takes place in the lungs. There has been much interest taken recently in a group of leukæmia-like conditions—leuco-erythroblastic anæmia, chronic non-leukæmic myelosis, megakaryocytic myelosis with otosclerosis and erythro-leukæmia—in all of which there are present excessive numbers of megakaryocytes in the bone-marrow and also in the spleen, liver and lymphatic glands. The blood-platelets, however, are not increased; there is a tendency to hæmorrhages; there is no accumulation of megakaryocytes in the lungs; and the condition progresses to fibrosis of the bone-marrow, encroachment on the marrow-cavity by cancellous tissue, and increased density of the cortex of the bones. The giant cells are identical with those normally present in the bone-marrow to which are attributed the formation of platelets.

However they may originate, the blood-platelets are to be regarded as being a particulate secretion rather than as a cellular element of the blood. In considering thrombocytopenia, there has been considerable dispute as to whether the decrease in the number of platelets is to be attributed to diminished production or to increased destruction. In what is known as "idiopathic" throm-

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bocytopenia, the symptoms disappear in a very striking fashion after splenectomy. The explanation for this may be one of two things: (1) that the spleen inhibits the maturation of the platelets in the bone-marrow, or (2) that it removes the fully-developed platelets from the circulating blood.

Troland and Lee (1938) found that a substance contained in the spleens of patients suffering from thrombocytopenic purpura had, when introduced into the circulating blood of normal rabbits, the effect of reducing the platelet-count by 90 per cent. For this substance, the name "Thrombocytopen" is suggested.

In connection with this matter of blood-platelets, it is expedient here to refer to the theory of Howell with regard to coagulation of the blood. It is epitomised by Whitby and Britton (1937) as follows:—

"Howell states that calcium ions by themselves can change prothrombin into thrombin without any action on the part of disintegrated platelets or tissue juices. In circulating blood the change is prevented by an anti-prothrombin known as heparin. This substance may be prepared from the liver by a complicated method, and if added to blood in vitro will prevent clotting for several days. Many authorities, however, do not believe that heparin is present in normal circulating blood. During the process of clotting heparin is neutralised by the thrombokinase (or cephaline) from the destroyed platelets." Howell's view of the mechanism of coagulation may be summarised thus:

"Prothrombin + calcium ions = thrombin.

Prothrombin + calcium ions + heparin = no thrombin.

Prothrombin + calcium ions + heparin + cephaline = thrombin.
(neutralise)

Thrombin + fibrinogen = fibrin."

Whatever theory be adopted, blood-platelets must be present before the phenomenon of blood-coagulation can occur. They are also intimately concerned with the occurrence of clot-retraction. A study of this phenomenon may furnish important diagnostic information with reference to post-arsphenamine blood-dyscrasia. When the platelets are well below the normal number, coagulation may still take place but the clot is soft, friable, and does not retract. Platelets may be greatly in excess of normal, but if there is a lack of fibrinogen, clot-retraction will be poor. Dearth of platelets also causes a prolongation of bleeding-time.

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Purpuric eruptions, indicative as a rule of thrombocytopenia, were recorded as occurring in both treated and untreated syphilis before the advent of arsphenamine. Prenatal syphilis occasionally gives rise to purpura neonatorum. I have seen an instance of *purpura annularis telangiectodes* (Majocchi's disease) in a man suffering from untreated tabes dorsalis. Petechial lesions may occur after the administration of iodides; and mercurial purpura has also been described. The same condition has also been recorded as supervening upon the administration of bismuth. It would appear that syphilis, mercury and the iodides, in causing purpura act chiefly upon the capillary endothelium, increasing the permeability of these vessels. To a much less degree they may exert some damaging effect upon the non-cellular elements of the blood-coagulation complex—and here, the platelets are considered to be non-cellular even though it be accepted that they are derived from megakaryocytes. The influence of the arsphenamines upon the bone-marrow will be discussed presently, but in the meantime it may be expedient to refer to certain other etiological factors.

Castex (1924) came to the conclusion that post-arsphenamine purpura was sometimes due to the toxic action of the arsenical agent upon the spinal cord. Eliet (1933) described two cases in which serious reactions followed the use of arsphenamine; and he considered that the arsenic, because of its elective action on the sympathetic nervous system, was the cause. In reporting a case of nitritoid crisis followed by severe hæmatemesis and hæmoptysis after small doses of neo-arsphenamine, Kosioulas (1933) was of the opinion that this agent caused a vagus-sympathetic disturbance. Sezary and Duruy (1933) report the case of a woman of hæmorrhagic diathesis (very excessive menstrual flow) who received "914" and developed purpura with hæmorrhage. Treatment was stopped and 8 months later she was given 0.15 gram of "914" which produced a nitritoid crisis and 4 hours later another attack of purpura with hæmorrhage. At this time there was found imperfect clot-formation and clot-retraction. These authors consider that this purpura was due to a disturbance of the sympathetic nervous system. They quote the case as an example of so-called "anaphylactic" purpura. It differs from

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dyscrasic purpura in that it is unaccompanied by serious blood-changes.

It would seem that sometimes platelet-reduction is brought about by arsphenamine in the peripheral circulation without there occurring any specific toxic action on the megakaryocytes of the bone-marrow. Rich (1933) described a case of this kind in which, after the administration of neo-arsphenamine, the patient developed generalised purpura with the blood-platelets markedly diminished in number. He considers that in this case the destruction of platelets must have taken place peripherally because their prompt reappearance in the blood-stream 4 days later rules out the possibility of any damage having been inflicted upon the bone-marrow.

Nevertheless, the balance of evidence goes to show that while the lesser degrees of blood-dyscrasia—mild and moderate thrombocytopenia—may be brought about by increased permeability of the capillaries, by interference with thrombin and fibrinogen and by peripheral destruction of platelets, there is probably present in the majority of cases some damage to the bone-marrow. When this progresses sufficiently far, the cellular elements of the blood become involved and the result is that various degrees of granulocytopenia are produced.

When the number of platelets in the peripheral blood falls below the critical level of 40,000 per c.cm., purpura almost invariably follows. When it occurs with the platelets well above that level (as in Cases 5, 6 and 11 of the present series) some other factor must be operative. The ages of these patients were 52, 49 and 51 years respectively; and this suggests that after the age of, say, 45 years, syphilis plus increasing senescence may tend to give rise to vascular permeability. There may, of course, have been some interference with the blood-coagulation complex also.

The etiological factors would seem to fall into two groups:—

- (1) Where there is a combination of increased vascular permeability plus a deficiency of prothrombin plus a decreased amount of fibrinogen brought about, severally and collectively, by syphilis or arsphenamine or both; and
- (2) Where damage has been done to the bone-marrow by arsphenamine.

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In each of the cases in this series where a blood-examination was carried out, there was found to be a reduction in the number of platelets. It may, therefore, be permissible to assume that the chief factor in causing post-arsphenamine blood-dyscrasia is damage to the bone-marrow.

The literature on post-arsphenamine blood-dyscrasia up to the year 1932 was reviewed by Loveman (1932) and by McCarthy and Wilson (1932). Their papers have been epitomised by Moore (1933), who, as already mentioned, divides the blood-dyscrasias into four classes. Moore analyses the 70 cases this manner :—

TABLE I

Dyscrasia	No. of Cases	No. of Deaths	Death-rate %
Thrombocytopenia . . .	12	—	—
Granulocytopenia . . .	15	5	33·3
Thrombo-granulocytopenia	7	1	14·2
Aplastic anæmia . . .	36	29	80·5
Total	70	35	50·0

According to the authors mentioned, *thrombocytopenia* supervenes immediately or from a few hours to a week after an injection of arsphenamine. *Granulocytopenia* has a more gradual onset, and symptoms may not appear until several weeks after the discontinuance of the drug. Sloughing of the oral and pharyngeal tissues may occur with an accompanying brawny œdema of the neck (agranulocytic angina). About 30 per cent. of cases of granulocytopenia are associated with jaundice or dermatitis. *Aplastic anæmia* appears between one and thirty days after the last injection of arsphenamine. The clinical picture is made up of fever, purpura, bleeding from mucous surfaces, necrotic pharyngeal angina, often in association with jaundice, dermatitis and extreme prostration.

If the cases analysed by Moore are re-grouped according to the classification I suggest, we have the following :—

TABLE II

Dyscrasia	No. of Cases	No. of Deaths	Death-rate %
Thrombocytopenia . .	12	—	—
Granulocytopenia . .	58	35	60·3
Total	70	35	50·0

This Table shows how necessary it is to diagnose and to treat post-arsphenamine blood dyscrasia in the stage of thrombocytopenia, otherwise it may progress to agranulocytosis which has the high death-rate of 60·3 per cent.

WHITECHAPEL SERIES

In the literature of syphilis there seems to be general agreement that injuries to the hæmatopœitic system are uncommon. It has, however, been pointed out by Stokes (1934) that this belief would probably require modification if periodical blood examinations were done upon patients showing malaise, pallor, pruritus and purpura during arsphenamine therapy.

Table III shows the incidence of post-arsphenamine blood dyscrasia at the L.C.C. (Whitechapel) Clinic during the four-year period from 1934 to 1938.

TABLE III

Sex	No. of Syphilis Patients	No. of Cases of Blood Dyscrasia	%
Males	2,167	7	0·323
Females . . .	1,083	6	0·554
Total	3,250	13	0·4

The incidence at Whitechapel is much higher than is usual ; but even there, this complication is not a common one. It is, however, important because of the fact that it causes a long and anxious period of invalidity which frequently has a fatal termination. The difference between the incidences for the two sexes is not a significant one.

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Until 1st January, 1937, the routine course of treatment for syphilis at Whitechapel Clinic extended for 13 weeks. It consisted of two unit-courses of 5 weeks each, separated by an interval of 3 weeks during which potassium iodide was given. In each of the unit-courses, there was given on the first day of each 7-day period an intravenous injection of neoarsphenamine and a deep subcutaneous injection of bismuth oxychloride; on the fourth day of each week sulpharsphenamine was given along with bismuth oxychloride. At the end of the 13 weeks, there was a rest period of 8 weeks during the last 3 of which the patient received potassium iodide. Further courses were carried out according to the clinical and serological indications.

Before describing and commenting upon the cases in this series, it is desirable to have some formula which will, in a practical manner, express what may be termed "intensity of therapy." The difficulty in this matter is that in this series under review, the duration of therapy and the amount of drug given, vary within very wide limits. So it is that in order to make comparisons, it is necessary to resolve the two factors—total amount of drug and time taken to administer that amount—into an "Intensity Index." This has been done by taking the total amount in grams, multiplying it by the arbitrary figure of 100 and dividing the result by the number of weeks from the first injection to the last.

CASE NO. 1 (A.2516), MALE, 53, SERO-POSITIVE PRIMARY :

Had 3 unit-courses of Neo., Sulph. and Bi. with KI. in intervals. After 2nd course had pain in upper chest. During 3rd course had arthritic pain in right shoulder and was "feeling seedy." 4th course begun. Had received 0.30 gram Sulph. and 0.90 gram Bi. when, 4 days after last injection, purpuric spots appeared on legs, forearms, face, lower lip and inside left cheek. Next day purpuric spots on tongue. Month later spots practically gone, but on receiving a scratch there was subcutaneous extravasation of blood. No record of blood picture. Diagnosis: *Thrombocytopenia* (mild).

The total amount of Sulph. plus Neo. given in 32 weeks was 12.45 grams, giving an Intensity Index of 38.9. No blood examination was done but the case may, on clinical grounds and from a consideration of the other cases in the series, be regarded as one of mild thrombocytopenia.

CASE NO. 2 (B.6582), MALE, 42, SERO-NEGATIVE PRIMARY :

Had 2 unit-courses of Neo., Sulph. and Bi. During subsequent interval while on KI., developed erythematous rash on forearms which

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was interpreted as an occupational dermatitis. General arthritic pains. 3rd unit-course given. KI. in following interval. 4th course begun. After 0.30 gram Sulph., Ehrlich test was positive. Continuation with Bi. alone. 21 days after last arsphenamine injection, purpuric rash on feet, ankles and legs. Pains in long bones at shoulders, elbows, knees and ankles. Sodium thiosulphate given. Bone pains became worse. Bled freely from site of buttock-injections on 16th day after purpura appeared. Much bruising. Admitted to hospital on 18th day of eruption. Blood-picture while in hospital :

	On Admission	4th Day	8th Day	12th Day
Erythrocytes . . .	2,000,000	1,600,000	2,200,000	1,300,000
Hæmoglobin . . .	36%	28%	35%	27%
Colour index . . .	0.9	0.9	0.8	1
Leucocytes . . .	2,200	2,200	880	920
Platelets . . .	100,000	Very scanty	Very scanty	Very scanty
Polynuclear neutrophils . . .	35%	29%	9%	5%
do. eosinophils . . .	2%	0.5%	Nil	Nil
Small lymphocytes . . .	59%	47.5%	56%	66%
Large do. . .		17.5%	34%	28%
do. hyaline cells . . .	3%	5.5%	1%	1%

There was some anisocytosis and poikilocytosis. Soon after admission, temperature rose to 105° F. where it remained. Gums bleeding. Petechiæ palate and fauces. None on conjunctivæ. Purpuric spots all over body. On 7th day, blood transfusion of 650 c.c. On 14th day large necrotic sloughs on uvula and fauces. Hæmatoma buttock. Gums and tongue oozing blood. Extensive subconjunctival hæmorrhages. Semi-comatose. Respiratory distress. Double incontinence. Blood transfusion of 600 c.c. Died 2 hours afterwards. The autopsy findings were broncho-pneumonia, severe anæmia with purpura and little regeneration of bone-marrow. There was reddish-brown marrow in the neck of the femur and in subcortical areas in upper third of shaft of femur. There were two small flecks in middle third of shaft. Beneath the corticalis of the whole of the shaft of the humerus there were a few distinct similar reddish-brown areas—these being larger in the upper fourth. Throughout the vertebræ, sternum and ribs, red marrow was present. Free iron was present in the liver and spleen but not in the kidneys. The spleen was only slightly enlarged, the cut surface was firm and blackish-purple in colour showing distinct Malpighian bodies.

Diagnosis : *Granulocytopenia* (severe).

This patient had Sulph. plus Neo. in the amount of 9.20 grams in 36 weeks, giving an Intensity Index of 25.5. The dermatitis was possibly a mild arsenical one and not occupational as it was thought to be at the time.

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CASE No. 3 (B.12090), MALE, 58, ENDOSYPHILIS :

Neo. omitted from 1st course ; Sulph. and Bi. given. Ehrlich positive. In 2nd course, Sulph. and Bi. only ; Ehrlich positive. Defaulted for 9 months. On return stated had had pleurisy. In next 6 months had Bi. only. Arthritic pains and prickling of feet. 3 months rest. Next course was Sulph. alone. Felt "seedy" for 3-4 hours after each dose. Defaulted for 2 months. On return had Sulph. for nearly 4 months. After this, 4 weeks rest and then Bi. for 2 months. Defaulted for 4 months ; on return, lumbar puncture. 5 months default. On return, Stab. for 4 weeks. 58 days after last injection developed purpuric spots on legs, feet, ankles, thighs and forearms. Arthritic pains, giddiness. Admitted to hospital where blood-picture was :

	On Admission
Erythrocytes	5,300,000
Hæmoglobin. . . .	82%
Colour index	0.77
Leucocytes	9,200
Platelets	50,000
Polynuclear neutrophils	75%
do. eosinophils	1%
Small lymphocytes	18%
Large do. . . .	2%
do. hyaline cells	4%

Diagnosis : *Thrombocytopenia* (moderate).

This man recovered after injections of sodium thiosulphate although it is doubtful if that agent can be credited with the result. He received 13.05 grams of Sulph. and Stab. in 188 weeks, which gives an Intensity Index of 6.4.

CASE No. 4 (B.19542), MALE, 41, NEUROSYPHILIS :

Had 1st unit-course of Neo., Sulph. and Bi. followed by 3 weeks of Bi. and KI. 2nd, 3rd, 4th and 5th unit-courses of Sulph. and Neo. Bi. was given in intervals. One day after last arsphenamine injection, purpuric spots on lower abdomen, back and thighs. Sodium thio-sulphate given. In 11 days purpura gone. Bi. recommenced. No blood-report available.

Diagnosis : *Thrombocytopenia* (mild).

This patient had 17.7 grams of Neo. and Sulph. in 48 weeks, which is equivalent to an Intensity Index of 36.8. He recovered in 11 days after sodium thiosulphate.

CASE No. 5 (B.22384), MALE, 52, ENDOSYPHILIS :

1st 3 months, Bi. only ; then KI. for 4 weeks. Next 2 months had Sulph. and Bi. concurrently. Four weeks rest, then 4 weeks KI. Neo.

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for 4 weeks. Two days after last dose, purpuric rash on legs, arms and tongue. Admitted to hospital where blood-picture was :

	On Admission
Erythrocytes	5,200,000
Hæmoglobin.	98%
Colour index.	0.94
Leucocytes	7,200
Platelets	120,000
Polynuclear neutrophils	67%
do. eosinophils	1%
Small lymphocytes	25%
Large do.	7%
do. hyaline cells	—

Diagnosis : *Thrombocytopenia* (moderate).

In hospital this case was given calcium lactate, glucose, adrenalin, and autogenous blood injection. His 3.5 grams of Neo. and Sulph. give an Intensity Index of 10.9.

CASE NO. 6 (B.26816), MALE, 49, SERO-NEGATIVE PRIMARY :

1st course Neo., Sulph. and Bi. for 4 weeks. Defaulted for 4 months. On return stated that 3 months after last dose spots appeared on legs from knees down. Jaundice 11 days after spots. When returned to Clinic, purpuric spots on feet and legs below knee and on forearms. Admitted to hospital where blood-picture was :

	On Admission
Erythrocytes	4,730,000
Hæmoglobin.	93%
Colour index.	0.98
Leucocytes	4,900
Platelets	130,000
Polynuclear neutrophils	43%
do. eosinophils	1%
Small lymphocytes	47%
Large do.	8.5%
do. hyaline cells	—

Diagnosis : *Granulocytopenia* (mild)..

This man received 1.20 grams of Neo. and Sulph. in 12 weeks, the Intensity Index being 10.0. The purpura appeared 77 days after the

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last arsenical injection. His blood-picture is that of a slight leucopenia, moderate thrombocytopenia with some relative lymphocytosis. In hospital he had 13 injections of sodium thiosulphate, adrenalin, glucose, liver extract orally and he was put on a fat-free diet. He recovered in 8 weeks.

CASE NO. 7 (B.15738), MALE, 14, PRENATAL SYPHILIS :

10 weeks Sulph. alone. KI. for 4 weeks. 10 weeks Sulph. alone. Rest for 8 weeks. KI. for 3 weeks. Sulph. alone for 12 weeks succeeded by KI. for 2 weeks (Iodism). Sulph. alone for 4 weeks and then 4 weeks of Bi. Rest for 6 weeks. Stovarsol tablets for next 2 years. Stab. for 12 weeks. In week following last injection purpuric spots on legs. Blood-picture :

	On Admission
Erythrocytes	4,900,000
Hæmoglobin.	94%
Colour index.	1.0
Leucocytes	5,000
Platelets	254,800
Polynuclear neutrophils	50.5%
do. eosinophils	2.5%
Small lymphocytes	33.5%
Large do.	6.0%
do. hyaline cells	7.0%
Mast cells	0.5%

Diagnosis : *Thrombocytopenia* (mild).

He received in 164 weeks 10.3 grams of Sulph. and Stab. plus 66 grains of Stov. Omitting the Stovarsol, the Intensity Index is 6.2, and if Stovarsol is included it might be rated as 10. This might possibly be an instance of pre-thrombocytopenia, the clinical condition being mainly due to some upset of the non-cellular elements of the blood-coagulation complex—thrombin, etc. He recovered after 4 weeks' treatment by orally given calcium lactate.

CASE NO. 8 (A.6559), FEMALE, 21, PRENATAL SYPHILIS :

1st course of Sulph. and Bi. Four weeks KI. During 2nd course of Sulph. and Bi. Ehrlich test became positive. Two months KI. Giddiness and slight nausea. Third course of Sulph. and Bi. One day after last dose, petechiæ on each buttock at sites of injections. A few spots over back and chest. Gums spongy and bleeding. Bruising on right shin. Admitted to hospital. Blood-pictures thus :

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	On Admission	3rd Day	13th Day
Erythrocytes . . .	4,900,000	4,400,000	5,200,000
Hæmoglobin . . .	80%	80%	94%
Colour index . . .	0.81	0.90	0.90
Leucocytes . . .	10,400	8,800	12,600
Platelets. . . .	Very scanty	?	Very scanty
Polynuclear neutrophils .	60%	64.5%	55%
do. eosinophils . . .	2%	1.0%	1%
Small lymphocytes . . .	} 34%	21.0%	25%
Large do.		5.0%	15%
do. hyaline cells . . .		8.5%	4%

Diagnosis : *Thrombocytopenia* (severe).

The 6.9 grams of Sulph. which this woman received in 32 weeks gives an Intensity Index of 21.8. Before going to hospital she was treated with calcium lactate and sodium thiosulphate. There are no notes as to treatment in hospital. She attended the clinic 3 months later, quite recovered.

CASE NO. 9 (A.6657), FEMALE, 26, ENDOSYPHILIS :

Began with 4 weeks KI. During 1st unit-course of Neo., Sulph. and Bi. the Ehrlich test became positive. Then there were 4 weeks of KI. Another course followed, the same as the 1st ; then another 4 weeks of KI., and a 3rd unit-course of Neo., Sulph. and Bi. This was succeeded by 4 weeks of Bi. when, again, the Ehrlich test was positive. KI. followed and then a month of Bi. KI. again for 4 weeks and then a unit-course of Neo., Sulph. and Bi. KI. was then repeated. There was then another unit-course of Neo., Sulph. and Bi. ; and this was succeeded by 4 weeks of KI. A Neo., Sulph. and Bi. unit-course was again repeated and so was a further 4 weeks of KI. A last unit-course of Neo., Sulph. and Bi. was given ; and 6 days after the last injection there was bruising all over the body with purpuric spots on neck, upper chest, forearms and over shins. There were no mouth lesions. Admitted to hospital. No reports available.

Diagnosis : *Thrombocytopenia* (mild).

This woman received 20.5 grams of Sulph. and Neo. in 72 weeks, the Intensity Index being 28.4.

CASE NO. 10 (A.6811), FEMALE, 24, SERO-NEGATIVE PRIMARY :

1st unit-course, Neo., Sulph. and Bi., followed by 4 weeks KI. In 2nd course, same as 1st, Ehrlich test became positive. " Hard lumps on legs " lasting a few days. KI. for 2 months, then 3 months of Neo., Sulph. and Bi. during which Ehrlich test again positive. KI. for next 4 weeks ; then 3 months of Sulph. and Bi. Rest for 3 months. Finally, 4 weeks of Neo., Sulph. and Bi. Day after last dose, petechiæ on both legs and in right antecubital fossa. Bleeding from gums. Admitted to hospital. No blood report available.

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Diagnosis : *Thrombocytopenia* (severe).

This woman had 14.55 grams of Sulph. and Neo. in 68 weeks, which gives an Intensity Index of 42.5. She was in hospital for 4 weeks.

CASE NO. 11 (B.2443), FEMALE, 31, ENDOSYPHILIS :

First course, 4 weeks Sulph. and Bi. In next 4 weeks, Bi. only. Next 6 weeks, Sulph. alone. 3 days after last dose, profuse purpura on legs. Much bruising. Bleeding from gums. Admitted to hospital. Blood transfusions on 8th, 10th and 32nd days. Blood-picture :

	8th Day	21st Day
Erythrocytes	1,940,000	2,700,000
Hæmoglobin	28%	43%
Colour index	0.7	0.8
Leucocytes	8,000	4,200
Platelets	5,000	?
Polynuclear neutrophils	70%	76%
do. eosinophils	1%	1%
Small lymphocytes	25%	17%
Large do.	2%	2%
do. hyaline cells	2%	4%

Marked anisocytosis, poikilocytosis and punctate basophila.

Diagnosis : *Thrombocytopenia* (severe) with a secondary anæmia due to hæmorrhage.

This patient received Sulph. only — 5.1 grams in 12 weeks, which gives an Intensity Index of 42.5. She was in hospital for 2 months.

CASE NO. 12 (B.4025), FEMALE, 51, LATE SECONDARY SYPHILIS :

Neo. for 10 weeks, followed by 7 weeks Bi. In 13th week there was considerable œdema and redness of right labium majus. Sulph. for 10 weeks, then Bi. for 5 weeks. This was followed by 7 weeks of Sulph. A few days after last injection purpuric spots appeared on arms and legs with scattered areas of bruising. Patient was not hospitalized. Blood-picture :

	1st Day
Erythrocytes	5,100,000
Hæmoglobin	70%
Colour index	0.68
Leucocytes	5,600
Platelets	193,000
Polynuclear neutrophils	58.5%
do. eosinophils	4.0%
Small lymphocytes	26.0%
Large do.	5.0%
do. hyaline cells	6.5%

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Diagnosis: *Thrombocytopenia* (mild).

The 18.6 grams of Sulph. and Stab. received by this woman gives an Intensity Index of 46.6—the highest in the series. As an out-patient she was treated with Ametox and Hepol. Although she had the greatest intensity of treatment in the series, she was the mildest case of blood-dyscrasia.

CASE NO. 13 (B.5709), FEMALE, 35, PRENATAL SYPHILIS:

From 1st October to 18th October, 1934, had Sulph. (0.9 gram), Neo. (0.45 gram) and Bi. Fainted after last injection of Sulph. From 22nd October to 5th November had Bi., then 3 weeks KI. Bi. from 29th November, 1934, to 3rd January, 1935. Rest with KI. till 19th March. From then till 23rd April had Bi. KI. for 3 weeks. From 21st May to 21st June had Bi. Mercurial pills from 9th July, 1935, to 2nd April, 1936. On 7th May, 1936, began weekly doses of Sulph. and Bi. which continued to 28th September, 1936. During this period complained of "pains all over body" and not feeling well after injections. On 29th September, had swelling and cedema of face. No nausea, vomiting or dermatitis. Hospital on 30th September with arsphenamine dermatitis. Improved on sodium thiosulphate. Took own discharge from hospital on 30th October. From 4th December, 1936, to 20th March, 1937, had Mist. Hydrarg. Iodid. From 10th April to 20th August had Bi. injections. Rest till 15th October, 1937, when began Stab. injections weekly till 13th January, 1938. Complained of red patches on skin which "come and go." Bi. from 22nd January to 8th February. On 15th February had 0.45 gram Stab. and 2 days afterwards purpuric patches on lower limbs. Ametox given and by 24th February the patches had practically gone.

Admitted hospital 26th February on account of (?) uterine fibroid. Final diagnosis: Microcytic anæmia (?). Early menopausal changes. Severe vaginal hæmorrhage. Uterus anteverted. Given Campolon. Blood-picture:

	3.3.38
Erythrocytes	2,790,000
Hæmoglobin.	47%
Colour index.	0.84
Leucocytes	2,500
Platelets	Not done
Polynuclear neutrophils	33%
do. eosinophils	—
Small lymphocytes	67%
Large do.	—
do. hyaline cells	—

Anisocytosis and slight poikilocytosis. Reticulocytes = 1%.

On 10th March discharged improved. On 13th March returned to Clinic with bleeding from gums and purpuric patches on feet. Hospital. Slight oozing from gums. Bruising on both feet and right hand. Her blood-pictures after her second admission to hospital were as shown:

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Case No. 13	On 2nd Admission	4th Day	6th Day	8th Day	11th Day	15th Day	17th Day	19th Day	23rd Day	27th Day
Erythrocytes .	I,430,000	I,900,000	I,780,000	I,720,000	I,920,000	I,690,000	I,700,000	I,950,000	I,680,000	790,000
Hæmoglobin .	27%	33%	41%	33%	25%	27%	33%	38%	25%	12%
Colour index .	0.95	0.87	1.1	0.97	0.66	0.8	0.97	1.0	0.72	0.76
Leucocytes .	I,750	500	I,350	750	900	I,500	600	I,000	I,100	I,500
Platelets .	5,460	10,000	7,000	5,000	8,000	10,000	10,000	10,000	10,000	Nil
Poly. neutrophils	18%	50%	22%	14%	16%	17%	8%	10%	14%	33%
Poly. eosinophils .										
S. lymphocytes .	81%	50%	78%	86%	84%	83%	92%	90%	86%	67%
L. lymphocytes .										
L. hyaline cells .	1%									

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Here we have a severe granulocytopenia with some of the features of aplastic anæmia. The blood-films showed anisocytosis and slight poikilocytosis.

This case contrasts strongly with the previous one. She received 9.45 grams of Sulph., Neo. and Stab. in 156 weeks, which gives an Intensity Index of 6—the lowest in the series.

On 29th March there developed purpuric lesions on inside of right cheek and on right tonsil. The autopsy showed a few petechial hæmorrhages in the skin. Small abscess right jaw. Interstitial keratitis. Trace fibrinous pleurisy both bases. Numerous petechiæ in peri- and endocardium. Slight fatty mottling of myocardium. Lungs congested; œdema and collapse at left base. Upper cervical glands were dark-red. Petechiæ in mucosa of stomach. Melanosis of colon. Liver and spleen œdematous and slightly rusty. Anæmia of pancreas. Kidneys showed pelvic hæmorrhage, anæmia and œdema with a few subcapsular petechiæ. Brain anæmic with small subarachnoid hæmorrhages over left Sylvian fissure. Petechiæ in cerebellum. Fatty marrow in sternum and vertebræ. Clot filling uterus and projecting into vagina. Hæmorrhage round gums. Fat bright yellow. Muscles rather red.

The series of cases consists of 7 men and 6 women. Among the men, the average age was 49—the youngest being 14 and the oldest, 58. Among the women, the average age was 30—the youngest being 21 and the oldest 51. Five patients—38 per cent.—were in the acute or early stage of syphilis, while 7—or 62 per cent.—were in the chronic or late stage. One factor was common to all—sulpharsphenamine. No case of blood-dyscrasia have I discovered where this agent has been withheld.

The prodromal signs in order of frequency were: positive Ehrlich test, arthralgia, malaise, giddiness, dermatitis, jaundice and bone-pains.

The average number of days between the last injection and the occurrence of purpura was 14—the shortest period being 1 day, and the longest 77 days.

There were 10 cases of thrombocytopenia—5 mild, 2 moderate and 3 severe. There were 3 cases of granulocytopenia—1 mild and 2 severe. The 2 severe cases were fatal. There was no relationship between the amount of drug given, the intensity of arsenical treatment and the occurrence of blood-dyscrasia. The 2 fatal cases had respectively received 9.2 grams in 36 weeks with an Index of 26, and 9.45 grams in 156 weeks with an Index of 6.0. The case with the highest Intensity Index of 47—Case No. 12—suffered the mildest blood dyscrasia. The average Intensity Index in the series was 33.

TABLE IV

Sex	Series No.	Clinic No.	Age	Degree of Syphilis	Drug used		Prodromal Signs			Types and Sites of Lesions										Thrombocytopenia				Granulocytopenia				Drugs used				Time during which As. given (weeks)	Total As. (gm.)	Intensity Index				
					Sulph. alone	Sulph. plus Neo	Sulph. plus Stab	Sulph. + Neo+Stab	Sulph. + Stab+Stovarsol	Giddiness	Malaise	Ehrlich +	Jaundice	Dermatitis	Arthritic pains	Bone pains	Bruising	Bleeding from Injection Sites	Bleeding from Mouth Lesions	Tonsillar and Facial Lesions	Facial Lesions	Trunk Lesions	Arm Lesions	Leg Lesions	Foot Lesions	No. of Days between last Injection and Symptoms	Mild	Moderate	Severe	Died	Recovered				Sulph.	Neo.	Stab.	Stovarsol.
Male	1	A2516	53	II	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4	+	—	—	—	—	—	—	—	—	—	—	32	12.45	38.9
	2	B682	42	I	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	21	+	—	—	—	—	—	—	—	—	—	—	36	9.20	25.5	
	3	B12090	58	V	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	57	—	—	—	—	—	—	—	—	—	—	—	188	13.05	6.4	
	4	B19542	41	VII	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	+	—	—	—	—	—	—	—	—	—	—	48	17.70	36.8	
	5	B22384	52	V	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2	—	—	—	—	—	—	—	—	—	—	—	32	3.50	10.9	
	6	B26816	49	I	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	77	—	—	—	—	—	—	—	—	—	—	—	12	1.20	10.0	
	7	B15738	14	VIII	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	7	+	—	—	—	—	—	—	—	—	—	—	164	10.30	6.2	
Female	8	A6559	21	VIII	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	32	6.90	21.5	
	9	A6657	26	V	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	6	+	—	—	—	—	—	—	—	—	—	—	72	20.50	28.4	
	10	A6811	24	I	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	68	14.55	21.3	
	11	B2443	31	V	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3	—	—	—	—	—	—	—	—	—	—	—	12	5.10	42.5	
	12	B4025	51	IV	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3	+	—	—	—	—	—	—	—	—	—	—	40	18.65	46.6	
	13	B5709	35	VIII	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2	—	—	—	—	—	—	—	—	—	—	—	156	9.45	6.0	
	Totals				2	7	3	1	1	3	4	5	1	2	4	1	6	2	7	5	2	5	9	11	2	Ave. = 14	5	2	3	1	2	11	2	—	—	—	—	—

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Combining the cases analysed by Moore with the present series, we have the following :—

TABLE V

Dyscrasia	No. of Cases	No. of Deaths	Death-rate %
Thrombocytopenia . .	20	—	—
Granulocytopenia . .	61	36	59
Total	81	36	44

Any condition occurring during or after arsphenamine therapy which has a death-rate of 59 per cent. is obviously one which must give the syphilologist furiously to think.

DISCUSSION

At the Salford Municipal Clinic, where I was Director for a period of eight years, 2,838 syphilis cases were handled ; but no case of arsphenamine blood dyscrasia was encountered. There, neo-arsphenamine, sulpharsphenamine, arsphenamine-diglucoside, bismuth and iodides were all in use, the only difference from the pre-1937 Whitechapel routine being that the arsenical and the bismuth were not given concurrently. That fact alone, however, does not seem sufficient to account for the absence of post-arsphenamine blood-dyscrasia in the Salford Clinic. On investigating the matter further, two additional differences were found : (1) At Whitechapel, *sulpharsphenamine was given as a routine to every syphilis patient* ; whereas at Salford it was only used when intravenous medication was impossible—a very low proportion of cases ; and (2) the brand of sulpharsphenamine used was different in the two Clinics. Experience at Salford showed that in general, sulpharsphenamine was prone to cause dermatitis ; and that some brands were, in that respect, worse than others. That brand which was found at Salford to be the least dermatropic, was not the one in routine use at Whitechapel.

Belding (1924) in 1924 directed attention to the high incidence of dermatitis following the use of sulpharsphenamine—16 per cent. of cases. Other workers found a lower incidence but still higher than with neo-arsphenamine. Schamberg and Wright (1932) mention purpura

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as being the most dreaded complication of sulpharsphenamine therapy ; and they consider that this drug has a particularly powerful anticoagulating effect upon the blood.

It is necessary to consider some of the chemical factors involved in the problem of post-arsphenamine blood-dyscrasia.

Arsphenamine-base has the formula :—

Formula A

Neo-arsphenamine is a formaldehyde-sulphoxylate-sodium (rongalit) derivative of arsphenamine-base and has the formula :—

Formula B

In this formula it will be seen that only one amino group (NH_2) is closed, the other remaining open. Apparently the French neo-arsphenamine preparations have both the amino groups closed, for, according to Fourneau (1925) they are represented by the formula :

Formula C

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This matter of open and closed amino groups has, it is suggested, a considerable bearing upon the sulpharsphenamines.

In 1912, under the German patent No. 249,726, there was registered an organic arsenical compound in which an amino group of arsphenamine-base was substituted by methylene-sulphonic acid. This would give the formula :—

Formula D

Levy-Bing, Lehnhof-Wyld and Gerbay (1919) in 1919 introduced "*Sulfarsenol*," and this was apparently identical with the German preparation just mentioned, for Harrison (1939) gives the above as the formula for it. As will be noted, only one of the amino groups is closed. In the most recent literature, however, issued by the manufacturers of Sulfarsenol (Laboratoires de Biochimie Medicale, Paris; British agents: Modern Pharmacals Ltd.) the drug is described as being "the sodium salt of the acid sulphurous ether of methylol-amino-arsenophenol" and the formula is given as :

Formula E

In the above, both the amino groups are closed. Formula E is that given in the British Pharmacopœia for Sulpharsphenamine.

The difference between Formula D and Formula E is comparable to that between Formula B and Formula C.

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Formula E is also that given by Voegtlin, Johnson and Dyer (1922) for the American sulpharsphenamine. There is a great deal of confusion and uncertainty with regard to the true formula of sulpharsphenamine and it would seem that Formula E has been adopted by the British Pharmacopœia as being a conventional one without any claim to strict accuracy, and that many manufacturers have adopted it in the same manner.

"*Sulphostab*," according to the makers (Boots Pure Drug Co. Ltd.) "may be regarded as disodium-dihydroxy-arsenobenzene-dimethylene-bisulphite." They state, however, that work by Dyke and King indicates that this structure requires modification, but that for purposes of comparison, Sulphostab may be regarded as being represented by Formula E—both amino groups closed.

"*Metarsenobillon*" is a sulpharsphenamine manufactured by Pharmaceutical Specialities (May and Baker) Ltd. They state that the exact composition of their product is unknown, but that there is evidence of it being a mixture of two, or perhaps three, closely related substances. They think it probable that Metarsenobillon is a mixture of the substance represented by Formula E with the following :

Dyke and King considered that the formula for sulpharsphenamine was :

but in 1935 they, as the result of further work, were of the opinion that commercial sulpharsphenamine conforming to B.P. 1932 corresponds approximately to a sodium salt of 3 : 3'-diamino-4 : 4'-dihydroxy-arsenobenzene-NNN'-trimethylene-sulphurous acid with the formula—

Another sulpharsphenamine is made by Burroughs Wellcome and Co. and is named "*Kharsulphan*." The formula for this is :

The sulpharsphenamine put upon the market in this country by Allen and Hanburys Ltd. and manufactured by the Diarsenol Co. Ltd. of Canada, is stated to be represented by Formula E. The makers state, however, that there is some difference of opinion as to its correctness and they therefore prefer to designate the product in terms of its manufacturing process, *i.e.*, "a compound formed by the successive condensation of arsphenamine, formaldehyde and sodium bisulphite."

There are, no doubt, various processes of manufacture of the different brands of sulpharsphenamine, and this may be the reason why some are more liable than are others to give rise to dermatitis and blood-dyscrasia. In America, where the incidence of such untoward effects was so high that in many quarters the use of sulpharsphenamine was given up, it would appear that the brands were of the type in which both amino groups were closed.

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The general impression is also gained that when a neo-arsphenamine of this type is used, more cases of dermatitis occur. This matter would seem to be worth while investigating statistically. All the 13 cases in the present series received a brand of sulpharsphenamine corresponding to Formula E.

From a general survey of the literature and a particular study of the 13 cases in the present series, the conclusions arrived at with respect to post-arsphenamine blood-dyscrasia are :

1. Although inorganic arsenic can give rise to blood-dyscrasia, this condition is more apt to occur subsequent to the administration of organic arsenicals, particularly those belonging to the diphenyl-nucleus group.

2. All sulpharsphenamines are much more prone to give rise to dermatitis and blood-dyscrasia than are arsphenamine, neo-arsphenamine or arsphenamine-diglucoside.

3. Some brands of sulpharsphenamine appear to be more potent than others in causing these untoward effects. It is desirable that these particular brands should be identified so that their use may be discontinued until such time as the manufacturers have eliminated their undesirable qualities.

4. The variation in the toxic effects caused by different brands appears to be related to molecular structure and this, in turn, to process of manufacture. It is eminently desirable that a greater degree of standardisation be brought into this group of remedial agents.

5. A preliminary step towards standardisation is a pooling of the British experience in respect of the incidence of dermatitis and blood-dyscrasia following the use of different brands. For this purpose a committee of inquiry might be set up.

6. The appearance of purpuric patches in a patient receiving any arsenical therapy for syphilis—but particularly a sulpharsphenamine preparation—is an indication for the withdrawal of the drug and for the performance of frequent blood examinations with special reference to platelets and granulocytes.

7. Prodromal signs calling for platelet counts are : positive Ehrlich test, arthritic pains, bone pains, malaise, giddiness, jaundice and dermatitis.

8. Pains at the ends of the long bones would seem to indicate severe bone-marrow damage.

9. The progress of events in these blood dyscrasias would appear to be : (a) *pre-thrombocytopenia*, where only non-cellular elements of the blood coagulation complex are affected ; (b) *thrombocytopenia*, as evidenced by the blood-picture but without clinical signs such as mucous or subcutaneous hæmorrhages ; (c) *purpura* ; (d) *bleeding from mucous surfaces* ; (e) *bruising* ; (f) *granulocytopenia* ; (g) *leucopenia* ; (h) *relative lymphocytosis* ; (i) *decrease of erythrocytes* ; (j) *fall in hæmoglobin* ; (k) *pharyngeal sloughing* ; (l) *death*.

10. It is prudent to have a blood examination carried out before beginning arsphenamine therapy. During treatment, this should be repeated upon the appearance of any of the prodromal signs enumerated above.

11. The occurrence of thrombocytopenia calls for daily blood examinations after the discontinuance of arsphenamine.

12. The occurrence of granulocytopenia calls for hospitalisation of the patient and the administration of nucleotide.

13. Post-arsphenamine blood-dyscrasia is unrelated to dosage but it tends to appear late in the course of treatment.

14. Its principal cause seems to be the action of the benzene radical upon the bone-marrow.

15. It would appear that the platelets in the peripheral circulation invariably suffer some damage from arsphenamine therapy. This may explain the mild cases of thrombocytopenia—the symptoms having too acute an onset to be likely to arise from bone-marrow damage.

16. When the marrow is attacked, the leucopoietic elements are the first to suffer—the earliest being the megakaryocytes which are the cells from which the platelets are derived.

17. As the attack progresses, the erythropoietic elements become involved, leading to a decrease in the number of red corpuscles with, in severe cases, some anisocytosis and poikilocytosis.

18. In severe blood-dyscrasia, the picture tends to be one of an overwhelming infection. Moore and Keidel (1921) have pointed out that these patients are very susceptible to other infections because the capability of the body for producing anti-substances, is largely resident in the bone-marrow.

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19. An index as to the progress of the case is to be found in the blood-picture. A progressive decrease of all the cellular elements with a relative lymphocytosis shows a very grave condition. When there are seen young polynuclears and reticulocytes, the prognosis is much more favourable.

It may have been noted with regard to some of the 13 cases described in this paper, that in many instances there is no record of the blood-picture or that it is incomplete. The explanation is to be found in the fact that these were hospitalised where effective contact between them and the clinic could not be maintained. All patients admitted to hospital on account of any untoward effect arising from anti-syphilitic therapy, should remain under the care of the Clinic—in other words, bed-accommodation should be provided at all large V.D. Clinics.

POST-SULPHONAMIDE BLOOD-DYSCRASIA

For a considerable time there have been used at White-chapel Clinic various sulphonamide preparations in the treatment of gonorrhœa. So far, no clinical instance of blood-dyscrasia has been encountered. A large number of hæmatological examinations have, however, been carried out upon patients receiving these agents; and from these, the general impression is gained that where there occur such symptoms as malaise, nausea, vomiting, jaundice and cutaneous eruptions, there are frequently found increased capillary fragility, prolongation of coagulation-time and bleeding time, and unsatisfactory clot-retraction. Only very rarely, however, if ever, is there any diminution in the number of blood-platelets.

What may—somewhat loosely—be termed the “mother-substance” of the sulphonamides is “*Sulphanilamide*.” This is represented by the following formula :

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Buttle (1939) states that sulphanilamide consists of a benzene ring, to opposite ends of which are attached an amino group and a sulphonamide group as is indicated above. From the chemical point of view, the derivatives of sulphanilamide can be divided into: (1) those in which the substituents are introduced into the amino group, and (2) those in which the substituents are introduced into the amide group.

"Prontosil" belongs to Class I and has the formula :

"Uleron" belongs to Class II and has the formula :

"M. & B. 693" also belongs to Class II and has the formula :

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"*Albucid*" is another member of Class II and has the formula :

All the aforementioned agents have been employed at Whitechapel Clinic.

Campbell (1938), in discussing the effect of the sulphonamides on the blood-picture, comes to the conclusion that the bulk of the evidence suggests that blood-dyscrasias are due to individual idiosyncrasy. He also considers moderate doses have the effect of mildly stimulating the bone-marrow.

Marshall and Walzl (1937) consider that the cyanosis which sometimes follows sulphonamide therapy is probably due to the formation of a pigment in the body from the condensation products of the drug. Sulphæmoglobinæmia is thought to be due to the union of intestinal sulphuretted hydrogen with the hæmoglobin. It is to be prevented by the avoidance of saline purgatives containing sulphur and by giving a low-residue diet excluding eggs, according to Archer and Discombe (1937) and to Paton and Eaton (1937). From their experiments on animals receiving sulphonamides, Webb and Kniazuk (1939) came to the conclusion that foreign pigments arise because of a disorderly production of compounds related to hæmoglobin, this being caused by indirect stimulation of the hæmatopoietic mechanism. Harris and Michel (1939) demonstrated the presence of methæmoglobin in the blood of 277 out of 467 patients receiving sulphonamide—roughly 50 per cent. They found that the average methæmoglobin-content was directly proportional to the concentration of the drug in the blood. These findings agree with those previously published by Wendle (1938) and by Campbell and Morgan (1939). Harris and Michel (1939) record, however, that the methæmoglobinæmia tends to diminish as the duration of therapy extends. They observed that it quickly vanishes

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when sulphonamide is discontinued ; and because of this, they consider that the pigment must be produced by oxidation of the hæmoglobin by a derivative of sulphonamide, and that it is reduced to hæmoglobin by the tissues. Its accumulation in the blood, therefore, depends upon the strength of these two factors. It was shown by Harris (1939) that a methæmoglobin-producing substance is formed in the tissues. He incubated a solution of sulphonamide with rat-liver and found that it acquired the property of changing hæmoglobin to methæmoglobin. With regard to these matters, it is interesting to note the views of McDonagh (1940) :

" . . . All invaders act alike and in a physical manner upon the host's main resistance, which resides in what I call the ' protein particles ' in the plasma. These protein particles are made to undergo first dehydration and then hydration. In the first, chemico-physical-change-activity, or energy, is liberated and is responsible for fever. In the second, chemico-physical-change-activity is conserved, and the particles use it for their own metabolism, instead of conveying it to the cells of the tissues and organs. The manifestation of disease resulting, and the area of the body where it appears, are regulated by the extent to which the cells are robbed of their power of activity. In this way, the hydrated protein particles become Public Enemy No. 1.

" Chemotherapeutic products are but invaders, and the action of them is twofold : to restore the dehydrated protein particles to normal, and to disperse the hydrated protein particles. The first action is effected through so-called positively charged atoms groups, what I refer to as radiating activity to the protein particles ; and the second action is through so-called negatively charged atoms or groups, attracting activity from the protein particles. Invaders act for the most part by attracting activity from the host's first line of defence. Robbing the protein particles of activity is reflected upon the red blood corpuscles, and the latter conserve their energy when the former undergo hydration. This step interferes with the red blood corpuscles acting as radiators of activity to the protein particles—the action I infer the latter to have. Certain of the oxygen atoms in the red blood corpuscles are intimately concerned in the exhibition of the radiation of activity, and they are prevented from acting in this way when the red blood corpuscles undergo hydration. The result of interfering with the part oxygen plays in the cycle of attracting, storing, and radiating activity, is to convert oxyhæmoglobin into methæmoglobin. Should the process extend to the depth of the red blood corpuscles, where sulphur plays the chief rôle oxygen plays on the surface, sulphæmoglobin is formed. Met- and sulph- hæmoglobin are, therefore, merely indicators of the extent to which the red blood corpuscles have been called upon to store their energy instead of attracting and radiating it. Energy is stored when the constituents become more firmly ' linked ' together. I use the term ' linked ' because most of the links in Nature are forged out of oxygen."

The *Lancet* in an annotation (1940) points out that there has been considerable difference of opinion as to

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the etiölogy and prevention of sulphæmoglobinaemia. Eggs have been prohibited and a low-residue diet prescribed. The egg-theory, however, appears to be based upon a misconception. While it is true that the bacterial decomposition of eggs outside the alimentary tract gives rise to sulphuretted hydrogen, yet in normal digestion the sulphur-containing amino acids are absorbed with very little sulphide-formation. It has never been shown that an egg-containing diet promotes the formation of sulphæmoglobin when the intestine is normal. The annotation points out that this also applies to other foods containing sulphur, many of which—*e.g.*, cheese—contain more than do eggs. Another prohibition which is sound—though not for the usually accepted reason—is that of Epsom and Glauber salts. These cause sulphæmoglobinaemia, not because the sulphates are reduced to sulphides, but *simply because they are purgatives*. Purgatives of any kind hurry the fluid contents of the small intestine into the colon; and it is the bacterial decomposition which takes place in these liquid fæces while in the colon which produces the sulphides. Certain drugs—of which phenacetin is one—predispose to the formation of methæmoglobin; and if even small quantities of sulphides are present, they give rise to sulphæmoglobin. Such drugs, therefore, must not be given along with the sulphonamides. Aspirin, however, is harmless. When administering sulphonamides, purgatives and phenacetin are to be avoided; but the patient should be permitted as normal a mixed diet as his general condition will allow.

Hewer (1940) drew attention to the fact that wounded persons with heavily infected wounds have, as a rule, received massive doses of some sulphonamide preparation. Many reach the operating theatre markedly cyanosed. This condition is due to methæmoglobinaemia and it cannot be relieved by inhalations of oxygen. To combat this cyanosis, an intravenous injection of 2.0 c.c. of a 1 per cent. solution of methylene-blue has been found effective, the cyanosis usually disappearing within 1½ hours after the injection. He also (1938) previously mentioned the possibility of an anæsthetic risk from the use of pentothal in patients who have been taking a sulphonamide agent.

In an interesting paper on "Porphyrinuria following Sulphanilamide," Rimington and Hemmings (1938) con-

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clude that a certain degree of blood-cell destruction is caused by this agent, but that the disturbance in pigment metabolism is not to be explained by this fact alone. They suspect a more deep-seated effect upon the hæmopoietic system, possibly analogous in some ways to lead-poisoning.

A large number of cases have been reported in which various cutaneous eruptions have supervened upon sulphonamide therapy. These appear to be invariably associated with blood-dyscrasia. Schlesinger and Mitchell (1938) consider that the steps in a sulphonamide eruption are: a prodromal fever, sometimes preceded by a transient leucopenia, followed by a morbilliform rash often with splenomegaly. The rash appears in from 5 to 17 days after beginning the drug and it lasts from 36 to 96 hours. Subsequent secondary leucopenia has been noted. Later administration of sulphonamide has been followed within a few hours by a scarlatiniform rash with fever and leucocytosis. Persistence with the drug has resulted in increased capillary fragility and sometimes arthritis. They observed that the passage of time, and increase of the dose for a short period, decreased or abolished these untoward effects.

Hallam (1939) reported a case of severe cutaneous and general reaction following M. & B. 693 and exposure to ultra-violet light. In this instance, the dose of the drug was a small one and the onset of symptoms occurred very shortly after a single exposure to the ultra-violet light. Hallam considers that the patient's skin was photosensitised by the sulphonamide and that exposure to the ultra-violet light precipitated the intense general and cutaneous reaction. Eidinow (1939) comments upon Hallam's report. His experiments show that the sulphonamides are sensitive to light as they are rapidly decomposed when solutions of them are exposed to ultra-violet rays. He has given to 22 patients receiving sulphonamide, general ultra-violet irradiation without any untoward effect. He suggests that in Hallam's case the erythema reaction produced by the ultra-violet rays may have aggravated the toxic symptoms following the administration of sulphonamide. Such reaction is, he states, quite independent of exposure to light; and he considers that rashes described as light-sensitisation by sulphonamides are not proven. In neither Hallam's nor

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Eidinow's communication is there any reference to the blood-picture.

Various other blood-conditions have been attributed to the sulphonamides, but the most important are those falling into the category of granulocytopenia. Gompertz (1937) reported a case occurring after 18 days of treatment with Prontosil. White cells numbered 300. There were no polymorphs, only lymphocytes. Erythrocytes and platelets were normal. In the *Medical Annual* for 1937, Davidson mentions the proneness of amidopyrine to cause granulocytopenia; and this point is well brought out by Plum (1937) in his excellent monograph. Prontosil flavum was responsible for a fatal case of granulocytopenia reported by Borst (1937) and here also the platelet count was normal. Cases have been reported by many other workers. An excellent paper on sulphonamide granulocytopenia is that by Jennings and Southwell-Sanders (1937). Levitt (1940) drew attention to the danger of granulocytopenia resulting from administering the sulphonamides in association with or following X-ray therapy, especially where large areas have been irradiated. A rapidly fatal case of granulocytopenia following small dosage—4.5 grams of sulphapyridine and 4.5 grams of sulphanilamide—administered during four days was recorded by Spain (1940). In this particular patient there was, apparently, no idiosyncrasy towards the sulphonamides. Where such an idiosyncrasy exists, the sensitising dose may be very small indeed; and, as McGrath (1940) points out, once a patient is sensitised, a small further dose (5 grains) might precipitate a fulminating attack of granulocytopenia. McGrath mentions the danger of allowing any drugs belonging to this series to be sold without control.

"A few tablets taken for a sore throat on casual medical advice, or without advice at all, might alternately result in the sensitisation of a number of persons. . . . There was some indication that metabolism and excretion might be hindered in some persons, with the result that the concentration in the blood became unduly high."

It would appear that the sulphonamides do not cause thrombocytopenia. All the recorded cases seem to come into the category of granulocytopenia, but in most of them no actual platelet-count was carried out. In the fatal case reported by Nicol and Freedman (1939), the number of platelets as judged from the ordinary stained film was normal. In respect of this apparent maintenance

of the normal platelet-count in cases of post-sulphonamide granulocytopenia, the suggestion naturally presents itself that the mechanism whereby that condition is brought about differs from that producing post-arsphenamine blood-dyscrasia. The difference would appear to be that while both sulphonamide and arsphenamine cause upset of the non-cellular elements of the blood-coagulation complex, increased capillary fragility and granulocytopenia, the former exercises no deleterious effect upon the platelets. While I do not hazard an opinion as to the reason why this should be, it is, I think, a point which must have some bearing not only upon treatment but also upon the diagnosis of an impending post-sulphonamide granulocytopenia. I am unable, likewise, to offer an explanation as to why post-arsphenamine blood-dyscrasia is apparently invariably accompanied by thrombocytopenia.

PREVENTION AND TREATMENT OF BLOOD-DYSCRASIA

Post-arsphenamine. When the arsphenamines are being given, prevention depends upon frequent hæmatological examinations with special reference to the platelet-count. A count of from 200,000 to 100,000 is a warning and calls for the withdrawal—at least temporarily—of these agents, and for their replacement by bismuthials.

When the platelets fall below the "critical level" of 40,000 the patient should be hospitalised, for he is heading for granulocytopenia. Liver extract, ordinary blood-transfusion and sodium thiosulphate do not seem to be of very much use except where anæmia is marked. Pentose nucleotide is of great value in most instances. This agent is issued in phials as an 8 per cent. solution; and 10 c.c. of this is given daily by the intramuscular route until definite improvement is registered. During the first four days of this treatment, the pentose nucleotide is also given intravenously in 100 c.c. doses, by diluting 10 c.c. of the solution with distilled water to a strength of 0.8 per cent. An index as to the progress of the case under this treatment is to be gleaned from the blood-picture. Where there is a progressive decrease of all the cellular elements accompanied by a relative lymphocytosis, the outlook is bad. When young polynuclears and reticulocytes appear, the prognosis is much more hopeful.

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Several cases of granulocytopenia have been treated with extract of yellow bone-marrow. In one patient who failed to respond to pentose nucleotide, the marrow extract caused the granulocyte count to rise from 3,500 to 7,500, the associated angina disappearing in 72 hours. Gorrie (1940).

Transfusions of blood from leukæmic patients have given good results in some cases. Pearson (1939) records an instance, however, in which this was unsuccessful although the donor's blood contained 120,000 white cells per c.mm.

Adenine sulphate—a degradation product of pentose nucleotide—has been used successfully in granulocytopenia ; and so also has ascorbic acid.

Irradiation-over the splenic area and splenectomy have brought about cure in some instances

Vitamin P gave a good result in a case of thrombocytopenia reported by Gorrie (1940).

Conclusions

(1) Sulpharsphenamine and sulphonamide are dangerous drugs and require most careful handling.

(2) The least toxic brand of sulpharsphenamine should be identified.

(3) Sulpharsphenamine should never be given if the intravenous route is available for the injection of neoarsphenamine.

(4) The sulphonamides, although of exceedingly high value in the treatment of gonorrhœa, have brought to the handling of that disease a very real element of danger, and it is essential to impress that fact upon those who are treating cases without having at hand the facilities for frequent hæmatological examinations.

(5) Special care is needed in patients suffering from syphilis and gonorrhœa when both arsphenamine and sulphonamide are employed.

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