POST ARSPHENAMINE PURPURA.

A review of thirty-six published cases, with personal observations on six hitherto unpublished cases.

by

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THESIS PRESENTED

FOR THE DEGREE OF M.D.

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PART I.

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POST ARSPHENAMINE PURPURA.

SECTION I.

(A) A GENERAL CONSIDERATION OF PURPURA HAEMORRHAGICA.

The term purpura is used to denote small haemorrhages into the skin, mucous membranes, and internal parts of the body. Purpura itself is not a disease, but rather a manifestation of one or more pathological influences at work within the body.

The outstanding feature of purpura haemorrhagica is bleeding from the mucous surfaces.

Certain blood investigations may assist in the elucidation of this particular type of purpura, such as

(1) The Thrombocyte count.

(2) Measurement of the bleeding time.

(3) The capillary resistance Test.

(4) Inspection of the blood clot for retraction.

Of these, the one which has given rise to most discussion is the first, which in cases of purpura frequently shows the presence of thrombocytopenia.
The present position can be summarised by saying that, whatever their relative significance, both the platelets and the vessel wall are intimately concerned in purpuric haemorrhage.

It is generally agreed that in the allergic subject, excessive sensitisation of the subject exists, and from this it might be argued that excessive sensitisation of the capillary wall exists in some people, and that purpura might be regarded as a purely allergic manifestation.

But the direct cause of the damage to the endothelium of the vessel wall in purpura haemorrhagica is still a matter of doubt. A significant reference has been made by Kidd (1928) to the frequency of a focus of infection in a series of cases, in which he suggests the purpura was due to a streptococcal infection, producing a mild toxaemia.

Many observers adhere to the view that purpura haemorrhagica is a clinical entity, caused by a diminution in the number of platelets. While it is true that arsenical treatment does cause a temporary fall in the number of platelets (Rosahn and Pearce 1934) there is not sufficient evidence to show that this is the primary cause of haemorrhage, or rather there is much evidence to prove that a decrease in the number of platelets is not the essential cause of purpura following the administration of arsenobenzol compounds.

If the occurrence of haemorrhage is due to a fall in/

in the number of circulating platelets, then it follows that the cessation of haemorrhage should result in an increase in platelets.

Discussing this point Hunter (1928) states that "it has not been satisfactorily demonstrated that thrombopenia always precedes the purpura, or that a platelet rise is a precursor of the arrest of haemorrhage."

Foerster (Tidy 1928) describes a case where the cessation of haemorrhage actually preceded a rise in the number of platelets. Mackay (1931) states that in purpura haemorrhagica the platelets are found in some cases diminished, and in others increased. MacKay also found that in cases where toxaemia existed, a reduction in the number of platelets was a frequent occurrence, and that a spontaneous increase occurs, whenever the toxic factor is removed.

Platelets have been made to disappear from the circulation, by the injection of ante-platelet serum, without the event of haemorrhage occurring.

Tidy (1928) suggests that in considering the pathogenesis of purpura four structures fall to be considered (1) platelets (2) spleen (3) bone marrow (4) endothelium.

With regard to platelets, it would appear from a mass of evidence that these bodies are diminished in/

in some way when haemorrhage takes place, but as has been pointed out reduction in platelets prior to the onset of haemorrhage has never been proved, although a diminution in platelets appears to accompany the haemorrhage.

If we admit that this reduction does take place, then two views fall to be considered: (1) that of Kaznelson (1919) who thinks that there is a hyper-destruction of platelets due to overaction on the part of the spleen and (2) that of Frank (1925) who considers it due to a fundamental defect in their production in the bone marrow.

These theories are both based on the assumption that there does exist in purpura haemorrhagica an actual reduction in the number of platelets, and that this reduction is responsible for the haemorrhage. However platelets can be absent from the circulation without the occurrence of haemorrhage and we must therefore look elsewhere for an explanation.

The spleen can only influence the haemorrhage through the platelets and as the same might be said of the bone marrow, we may take it that neither of these structures are implicated in the direct cause of haemorrhage.

With regard to the endothelium, increased permeability or fragility is the only cause left for consideration. It would seem that so long as the endothelium is intact no haemorrhage can take place.

In/

In this connection the researches of Bedson (1922) are important. He was able to demonstrate two factors which give rise to haemorrhage, (1) injury to the endothelium caused by injection of serum, and (2) reduction of platelets produced by injection of agar serum. It is a significant fact that neither of these alone produced haemorrhage. It would seem that if the endothelium remains intact no haemorrhage will occur even in the absence of platelets, but when the endothelium is damaged the deciding factor will be the number of platelets available for protection, and the maintenance of supply.

Several observers have noted a toxaemic factor present in their cases of purpura haemorrhagica, and have attributed to this factor a possible cause for the onset of purpuric symptoms. This theory has not yet been very extensively studied and appears not to have impressed or interested any of the observers who have studied cases of purpura haemorrhagica following the administration of arsenic. It is to add further evidence to this theory that this thesis is mainly concerned.

B./

(B) CLASSIFICATION OF POST ARSPHENAMINE PURPURA.

In order to classify post arsphenamine purpura as a clinical entity a good deal of confusion has arisen in the attempt, and such classification as now exists presents a somewhat complex and confusing picture.

This is principally due to the fact that arsenical therapy has a depressing effect on the bone marrow which varies to a very great extent. Where a comparatively small amount of arsenic has been administered one may find evidence of a profound toxic action on the bone marrow, and where large doses of arsenic have been given over a long period of years, the only evidence of toxic effect may be a few purpuric spots with none of the other accepted signs of purpura haemorrhagica present.

Various observers have endeavoured to establish a new classification of purpura haemorrhagica.

W.R. Kennedy (1928) suggests three groups:-

(1) Purpura without haemorrhage.

(2) Purpura with haemorrhage.

(3) Aplastic Anaemia with haemorrhagic diathesis.

This observer states that in group (1) a purpuric eruption is present, but no haemorrhage from the mucous membrane takes place. He also states that in group/

group (2) there is a marked decrease in the number of platelets, and also a prolongation of the bleeding time with non-retraction of the blood clot.

Dodd & Wilkinson (1928) have added another group - the agranulocytic cases. These authors review 24 cases of this type of blood dyscrasia. It is of interest to note that in their own reported case, an acute tonsillar infection was found to be present in the early stages of this complication.

Fairley (1930) believes that the type of Purpura Haemorrhagica seen is dependent upon the degree of bone marrow depression. As arsenic does not always depress equally the elements of the haemopoietic system, it therefore follows that the clinical picture will vary in individual cases. In Fairley's case - which was fatal at the 12th day - an ischio rectal abscess was discovered. Premonitory symptoms were well marked in this case.

Loveman (1932) states that where the arsphenamine attacks only the platelets we get purpura, and depending upon the degree of intoxication we may have either simple purpura, purpura with haemorrhage, or if the bone marrow is involved purpura with aplastic anaemia.

McCarthy and Wilson (1932) suggest that there are three main groups into which most cases can be placed.

(1) Thrombocytopenic group.

(2) The granulocytopenic group.

(3) The aplastic group.

"The characteristic feature of Group 1 is the thrombocytopenia. Here there is usually very little interference with the bone marrow function, and there is no extreme degree of anaemia, unless of course haemorrhage is severe." It would appear as though this group stands apart as a clinical entity and no explanation of this particular type of purpura has yet been advanced. But no hard and fast line can be drawn for there are other cases which although thrombocytopenia is a marked feature they show a certain degree of granulocytopenia.

Groups 2 and 3 are closely related - both groups show depressed bone marrow function - the difference between the two depending on the extent to which the white cell production has been involved.

Although the histological and pathological picture varies greatly in these groups, the clinical picture is sometimes confusing. It is often impossible to make a diagnosis between the three groups without an examination of the blood film or a bone marrow puncture.

Agranulocytosis and aplastic anaemia are already definitely established diseases, and with these we are not directly concerned, except in so far that thrombocytopenic purpura haemorrhage following the administration of arsenic may closely simulate if not actually merge into the granulocytopenic and aplastic groups.

It may well be that post arsphenamine purpura is merely/

merely part of a more complex disease, and that the blood picture obtained in any given case depends upon the extent of damage done to the bone marrow. Even if that be so, the inclusion of such cases as McCarthy and Wilson's groups 2 and 3 does not materially help to solve the phenomenon of purpura haemorrhagica after arsenical treatment.

There is no doubt that following the administration of arsenic all degrees of bone marrow damage can occur. In some cases there is no clinical evidence at all of purpura haemorrhagica, and the only indication of some pathological process at work is the presence of gross damage to the bone marrow, such cases are naturally labelled agranulocytosis or aplastic anaemia. But again there may be all the clinical signs of purpura haemorrhagica present, with very little evidence of bone marrow damage.

Although haemorrhage into the skin and mucous membranes may occur with extreme bone marrow damage, one frequently finds that where haemorrhage is severe the bone marrow most frequently escapes. We know that toxins of whatever origin have a selective affinity for different tissues, and the same toxin acting at different times does not always attack the same tissue. It is therefore reasonable to argue that arsenic may at one time attack the endothelial lining/

lining of the blood vessels, at another time it may select the bone marrow, or at still another, affect both of these structures. It therefore follows that while haemorrhage in the form of purpura, may be the only sign of some pathological process at work in one patient, a blood picture indicating gross bone marrow damage may be the salient feature in another patient.

SECTION II.

THE DRUG.

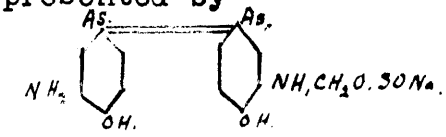
After many years of search for an efficient spirochaeticidal agent which could be used clinically Ehrlich and his co-workers discovered "arsphenamine" in 1901. As it was the 606th product in the series being investigated it soon became known as 606 and the patent name given to it of salvarsan. The term arsphenamine came into use during the World War 1914-18 when the drug was manufactured in the U.S.A. Synonyms for it include arsenobenzol and diarsenol. The administration of salvarsan was associated with many technical difficulties so that Ehrlich continued his researches to discover neo-salvarsan as the result of his 914th test. Present day synonyms for this are novoarsenobenzol, neo-arsphenamine (U.S.P. and B.P.) Proprietary manufacturing chemical firms have added their own distinguishing labels e.g.

Novoarsenobillon is neoarsphenamine made by May & Baker.

Neokharsivan " " " " Burroughs Wellcome and Co.

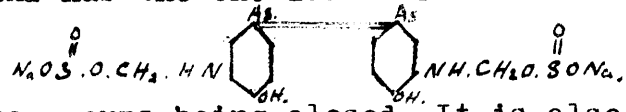
Stabilarsan/

Stabilarsan is an arsphenamine compound made by Boots in which arsphenamine is combined with glucose, but in dosage and action is equivalent to a neoarsphenamine derivative. Neoarsphenamine is sodium 3.3 diamine 4 4 dihydroxyarsenobenzene methanal sulpoxylate. Its formula is represented by



It contains 19-22 per cent of arsenic in the trivalent form and is a canary yellow powder dispensed in vacuum or nitrogen filled glass ampoules. The standard dose for a 12 stone man is 0.6 gm. given intravenously dissolved in 10 cc. of sterile water once weekly. Dose for a woman is from 0.15 to 0.45 gm. once weekly.

Sulpharsphenamine was developed in 1922 in the Hygienic Laboratory of the United States Public Health Service and has the chemical formula



both amino groups being closed. It is also a light yellow powder 19 per cent of trivalent arsenic but is relatively more soluble than any of the other members of "914" group and is suitable for intramuscular administration in a dose of 0.15 to 0.45 gms. dissolved in 1-3 cc. of sterile water, given once per week.

From a clinical point of view the action, both therapeutic and toxic, of all the above drugs is so similar that it is convenient to use the name "arsphenamine" as a comprehensive adjective e.g. post-arsphenamine/

post-arsphenamine purpura, and not necessarily specifying which particular brand of drug was used.

TOXICOLOGY.

In reviewing the literature on the toxicological aspects of the arsphenamines three factors at once emerge, namely, the arsenical content of the drug, the benzene component in the drug and the influence of allergy. Each of those or any combination of them may play a part in the production of post-arsphenamine purpura.

When it is considered that the maximum adult dose of "914" or its equivalent, introduces into the body an amount of arsenic approaching twenty-five times the fatal dose of inorganic arsenic, it is not to be wondered at that toxic effects are common.

Stokes (1934) states that the trivalent arsenicals have a special affinity for vascular structures such as the small arterioles and capillaries below the skin papillae.

Anwyl-Davies (1921) believes that the purpura is caused by damage to the capillary endothelium by the arsenic contained in the arsphenamine.

Osborne quoted by Stokes suggests that a large part of the injury produced by the trivalent arsenicals is associated with damage to the capillaries in whose walls extensive deposits of arsenic can be demonstrated.

Flandin and Tzanck (1922) believe that arsphenamine disturbs the normal coagulation of the blood. They report that the coagulation of the blood may be prolonged to thirty minutes and upwards following the injection of arsphenamine. They go so far as to suggest that arsphenamine is superior to citrate as an anticoagulant of the blood. These authors believe that arsphenamine acts upon the thrombin or its precursors and not upon the blood elements.

McCarthy and Wilson (1932) state that the arsphenamines appear to have at least two separate actions - one a depression of the bone marrow and the other a toxic action on the platelets. The question as to whether any one particular type of arsphenamine is more likely to cause purpura has not been solved.

Moore and Foley (1920) state that the most satisfactory theory is that there is some impurity in the drug which causes the purpura, or alternatively that under certain circumstances in the body, during the course of the metabolism of the drug, a substance is formed which leads to the development of purpura.

It is equally a matter for thought that the benzol radical is responsible for the development of purpura as all the arsenicals used in treatment contain the benzol radical, and there can be no doubt that purpuric symptoms do occur as a result of benzene poisoning. Nikulina and Titowa (1934) find thrombocytopenia very frequently among benzol workers (seventy-three out of seventy-six cases).

Selling and Osgood (1935) state that in chronic Benzene Poisoning, anaemia is an outstanding symptom. Petechial haemorrhages may occur, also nose bleeding or excessive menstrual period.

Rohner, Baldridge and Hansmann (1926) in an article on Chronic Benzene Poisoning instance the case of a male patient, with bleeding from the gums and rectum, and haemorrhages into the skin. In this case the haemoglobin was 20%. White cells 1,400. Platelets 70,000.

Observations carried out by Falconer and Epstein (1936) suggest that an allergic phenomenon is responsible for the complication, rather than some oxidation product, formed by the breaking down of neoarsphenamine in the body, as was first thought.

The accepted view seems to be that the fundamental basis for symptoms is the destructive action of the benzol radical on the haematopoietic tissues. If this were the only factor involved, it is not clear why only certain individuals develop purpuric symptoms. In view of the almost universal use of arsenic in the treatment of syphilis, one would reasonably expect this complication to be much more prevalent than it actually is, if only the arsenic was at fault. The incidence of purpura haemorrhagica is much too low for the benzol radical per se to be the only factor in the aetiology. Idiosyncrasy, or sensitisation, or some toxic factor may play a part.

SECTION III.

STUDY OF CASES REPORTED IN LITERATURE.

When one considers the almost universal use of arsenobenzol and its derivatives in the treatment of syphilis, it is very surprising that so few cases of purpura haemorrhagica have so far come to light. Labbe and Langlois were the first to draw attention to this serious complication of arsenical therapy in 1919.

It is hardly conceivable that such a very unusual complication could occur and pass unnoticed, or when observed should have passed without comment. Even if cases were overlooked by the medical staffs of hospitals and clinics, the symptoms of the complications are so unusual and come on with such suddenness, it is not likely that the patient would allow such symptoms to pass without remark. Therefore one is inclined to accept such cases as have been published, as approximately representing the true number which have occurred. No attempt has been made to review here every case of arsenical purpura which has been published. But a sufficient number of cases have been examined in order to reach some definite conclusion regarding the phenomenon.

Purpura may be regarded as a rare but serious complication in the administration of arsenic.

Cole and his co-workers (1931) observed only two cases out/

out of a total of 338 complications, their cases including over 78,350 injections of various arsenicals in 1,212 patients over a ten year period.

The Salvarsan Committee (1922) make no mention of purpura haemorrhagica as a complication of arsenical treatment in syphilis.

More recently Burke (1941) states that over a period of eight years 2,838 cases of syphilis were handled at the Salford Municipal Clinic, and no case of thrombocytopenia or indeed any state of Blood Dyscrasia occurred.

Again, at the Whitechapel Clinic during a four year period, 3,250 syphilitic patients were treated and there were only thirteen cases of Blood Dyscrasia, ten of these patients were cases of thrombocytopenia.

Bickford and Tilghman (1933) in reporting two cases of purpura haemorrhagica occurring in children with congenital syphilis state that their records show that out of 1,825 children treated over a period of eleven years, involving 25,950 treatments, only two cases of purpura haemorrhagica occurred, nearly every child was treated with neoarsphenamine.

Falconer, Epstein and Wever (1936) find only four cases of purpura haemorrhagica reported from the Syphilis Clinic at the University of California, where 60,000 treatments have been administered since 1924.

The/

TABLE I.

36 cases reviewed.

Case Nos.	Sex	Age	Drug	No. of Inject.	Pro-dromal Symp-toms.	Inter-val.	Hae.	Hb.%	Reds %	Whites %	Polys. %	Lympho-cytes %	Monos. %	Baso. %	Eosin. %	Plate-lets.	Result
1	F	-	Neo-arsphen	16	+	Not stated	++	-	1,601,000	4650	30	25	35	-	-	-	Died
2	F	50	"	10	+	6 hrs.	+	64	3,176,000	1100	11	84	-	-	5	Nil	Died
3	F	23	Novarseno-billon	8	-	12 hrs.	Nil	-	-	-	-	-	-	-	-	-	Rec.
4	F	51	Unknown	5	+	4 hrs.	+	-	-	-	-	-	-	-	-	-	Rec.
5.	M	37	Sulph-arsenol.	13	-	1 hr.	++	-	--	-	-	-	-	-	-	-	Died
6.	M	44	Neo-arsphen.	24	+	Immed.	+	-	-	-	-	-	-	-	-	-	Rec.
7.	M	54	Arsphenamine Sulphar-sphenamine	15	-	21 days	++	40	2,810,000	1900	16	80	0.4	-	-	175,000	Died
8.	F	26	Neoars-phenamine	17	+	1 hr.	++	-	-	-	-	-	-	-	-	60,000	Rec.
9.	M	30	N.A.B.	-	-	24 hrs.	+	80	3,200,000	1500	18	35	47	Nil	Nil	10,000	Died
10.	F	51	Neoarsphen.	30	-	11 days	+	-	3,400,000	3,000	4	88	-	-	-	50,000	Rec.
11.	F	28	Sulphostab.	25	Nil	10 hrs.	++	-	-	-	-	-	-	-	-	150,000	Rec.
12.	F	29	N.A.B.	10	+	7 days	++	55	2,630,000	2,500	2	92	2	4	-	180,000	Died
13.	F	38	Sulphostab.	18	+	5 days	+	86	5,760,000	5,800	62	25	11	1	1	42,000	Rec.
14.	M	55	N.A.B.	10	-	12 days	+	38	1,810,000	Lymphos. only (1700)	Nil	1700	-	Nil	-	Nil	Died
15.	M	49	Neoarsphen.	21	+	3 hrs.	+	75	4,500,000	7,000	67	27	1	-	5	Low	Rec.
16.	M	29	Neoarsphen.	23	+	1 hr.	+	-	4,500,000	6,200	44	-	-	-	-	Low	Rec.
17.	M	6	Neoarsphen.	70 (approx)	+	24 hrs.	+	86	4,700,000	7,800	-	-	-	-	-	Low	Rec.
18.	M	8	Neoarsphen.	13	+	1 hr.	+	80	4,290,000	7,000	67	31	-	-	-	Nil	Rec.
19.	M	33	Neoarsphen.	16	+	Few days	+	46	2,330,000	4500	76	14	4	-	6	Nil	Rec.
20.	M	48	Neoarsphen. Bismarsen	46	+	11 hrs.	++	-	Normal	Normal	-	-	-	-	-	Normal	Rec.

TABLE I. continued.

Case Nos.	Sex	Age	Drug	No. of Inject.	Pro-dromal Symp-toms.	Inter-val.	Hae.	Hb.%	Reds %	Whites %	Polys. %	Lympho-cytes %	Monos. %	Baso. %	Eosin %	Plate-lets	Result
21.	M	40	Sulph-arsphen	12	+	4 hrs.	+	42	3,000,000	24,000	87	10	2	-	1	Nil	Rec.
22.	M	34	Neoarsphen.	24	+	1 hr.	+	72	3,870,000	11,600	63	18	13	-	5	30,000	Rec.
23.	F	48	Neoarsphen.	- unknown	+	Few minutes	+	85	4,410,000	5,150	67	16	13	-	3	10,000	Rec.
24.	M	37	Neoarsphen.	6	+	3 hrs.	+	90	4,600,000	8,360	76	8	12	-	4	80,000	Rec.
25.	M	30	Neo-kharsivan	7	Not stated	18 hrs.	+	50	2,620,000	4,400	60	26	13	-	-	Nil	Rec.
26.	M	30	Neoarseno-benzene & Sulphar-senobenzene	14	Nil	5 days	+	102	5,180,000	-	-	-	-	-	-	30,000	Rec.
27.	M	53	Neoarsphen. sulpharsph.	16	+	4 days	Purpuric spots	-	-	-	-	-	-	-	-	-	Rec.
28.	M	58	Sulpharsph. Stabilarsan	50	+	58 days	Purpuric spots	82	5,300,000	9,200	75	20	-	-	1	50,000	Rec.
29.	M	41	Neoarsphen.	25	+	1 day	Purpuric spots	-	-	-	-	-	-	-	-	-	Rec.
30.	M	52	Neoarsphen. Sulpharsph.	12	+	2 days	Purpuric rash	98	5,200,000	7,200	67	32	-	-	1	120,000	Rec.
31.	M	14	Sulpharsph. Stabilarsan	48	+	7 days	Purpuric spots	94	4,900,000	5,000	50.5	39.5	-	-	2.5	254,800	Rec.
32.	F	21	Sulpharsph.	30	-	1 day	+	80	4,900,000	10,400	60	34	-	-	2	Very few	Rec.
33.	F	26	Neoarsphen. Sulpharsph.	35	-	6 days	+	-	-	-	-	-	-	-	-	-	Rec.
34.	F	24	Neoarsphen. Sulpharsph.	38	-	1 day	+	-	-	-	-	-	-	-	-	-	Rec.
35.	F	31	Sulpharsph.	10	-	3 days	+	28	1,940,000	6,000	70	27	-	-	1	5,000	Rec.
36.	F	51	Neoarsphen. Sulpharsph.	27	-	Few days	+	70	5,100,000	5,600	58.5	31	-	-	4	193,000	Rec.

\+ = moderate Haemorrhage.
++ = severe Haemorrhage.

Authors Reporting Cases Reviewed in Table I.

Case No.	Authors.	Date.
1.	Labbe & Langlois	(1919)
2.	Moore & Keidel	(1921)
3.	T. Anwyl-Davies	(1921)
4.	Florand, Nicaud & Froment	(1922)
5.	T.P. Buist	(1925)
6.	C. Morton Smith	(1925)
7.	F.C. Combes	(1927)
8.	W.R. Kennedy	(1928)
9.	M.M. Bocage and Le Filliol	(1929)
10.	B. Appel	(1930)
11-14	Bamforth & Elkington	(1931)
15-16	McCarthy & Wilson	(1932)
17-18	Bickford & Tilghman	(1933)
19.	A.B. Loveman	(1932)
20.	J.L. Grund	(1934)
21.	E.H. Hudson	(1935)
22-24	Falconer, Epstein & Wever	(1936)
25.	D.R. Gorrie	(1940)
26.	S.M. Laird	(1942)
27-36	E.T. Burke	(1942)

The foregoing table gives the blood findings in the cases reviewed. In nine instances however, no blood examination was carried out. In some other cases a blood examination was done each day for several days after the onset of purpuric symptoms. The result of blood examination carried out immediately following the onset of symptoms has been tabulated. In the following table Prodromal symptoms will be taken to indicate such reactions as the following: rash, malaise, nausea, headache, petechiae or bleeding into the skin or mucous membrane, bleeding from nose and gums, and vagina, nitritoid reaction, haematuria, melena, chilly sensation, vertigo.

Conclusions to be drawn from a study of the foregoing table:-

(1) Sex.

It will be seen that out of thirty-six cases reviewed twenty-one of these are males. There is very little evidence however to suggest that the complication occurs more frequently in any one sex. Seven cases died out of the total number, four of the seven deaths occurred in females.

(2) Age.

No special significance can be attached to the age factor. The common age group would appear to be between twenty years and fifty-five years.

The type of arsenical used in the foregoing thirty-six cases is given in Table II.

Neoarsphenamine was the drug most frequently administered. Next in order comes Neoarsphenamine combined with Sulpharsphenamine, then sulpharsphenamine alone.

TABLE II.

Drug.	No. of cases in which used.	%
Neoarsphenamine	19	54.3
Neoarsphenamine + Sulpharsphenamine	6	17.0
Neoarsphenamine + Bismarsen	1	2.9
Sulpharsphenamine	4	11.5
Sulpharsphenamine + Stabilarsin	2	5.7
Sulpharsphenamine + Arsphenamine	1	2.9
Sulphostab	2	5.7

It will be noted that Neoarsphenamine was used alone in 19 cases out of 35, Neoarsphenamine + Sulpharsphenamine was used in six cases out of 35, and Sulpharsphenamine alone in four cases. In one case the drug used was unknown. Neoarsphenamine or Sulpharsphenamine was therefore used in 82.8 per cent of the cases reviewed.

Whilst/

Whilst therefore neoarsphenamine appears to be the drug which most frequently gives rise to purpuric symptoms, this is probably because of its more general use, and had sulpharsphenamine been used to the same extent no doubt this latter drug would have given rise to a greater proportion of reactions.

(3) Number of Injections.

The average number of injections administered in each case amounts to about twenty.

It will be noted from Table I that in no case had the patient received less than five injections of arsenic before the onset of symptoms. On the other hand, one patient, a child aged six, received no fewer than seventy injections before the onset of purpura. In one case reported by Emile-Weil and Isch-Wall (1927) purpuric symptoms occurred after only two injections. This would seem to nullify the view held by some observers, that the arsenic has a cumulative effect or that a certain time must necessarily elapse before the drug exerts its toxic influence.
In view of the great variation in the number of doses given, it would appear that this is not a factor which influences the onset of post arsphenamine purpura. However it may be stated that, as a general rule, purpura following the administration of arsenic usually occurs after several doses of the drug has been given.

(4) Prodromal Symptoms.

In many cases after the advent of symptoms further doses of the drug were given. In twenty-two cases out of a total of thirty-six (61 per cent) prodromal symptoms of one kind or another were present. The percentage might even be higher as in a few instances no record is available as to whether prodromal symptoms were present or not. It is certain that had sufficient care been exercised in questioning the patients as to previous sensations after arsenical injections, some of these cases of purpura haemorrhagica could have been avoided. It would appear that once any untoward reaction occurs which might suggest an intolerance to arsenic on the part of the patient, the reaction should be regarded as a stern warning that no further arsenical preparations should be administered - not even after a lapse of years. A period of rest from arsenical treatment does not appear to bestow immunity or give further protection against any further reaction.

Various authors have commented upon this question of apparent sensitivity on the part of the patient.

Bickford and Tilghman report the case of a child aged six, in whom purpuric symptoms recurred after only the second injection of arsenic, the child having had no arsenic in a two year interval.

Falconer, Epstein and Wever report the case of a male/

male patient, aged 34, who received twenty-four injections of neoarsphenamine. No further arsenic was administered for thirteen months. On the recommencement of treatment, the fourth injection of neoarsphenamine was followed by a severe reaction with purpuric symptoms. In this case a year did not suffice to abolish the sensitivity to arsenic.

The chief points illustrated by these cases are:

(1) that neither the individual dose of the drug nor the number of doses administered over a prescribed period of time, has any direct bearing on the cause of the complication.

(2) that the sensitivity is not dependent upon the amount of the drug previously administered.

(3) that post arsphenamine purpura haemorrhagica is a complication which generally occurs only after repeated injections.

(4) that the patient appears to become in some way unduly sensitive to the arsenic.

(5) Interval between injection and onset of symptoms

Purpura haemorrhagica is an acute complication which appears with great suddenness. In the cases collected from the literature the average time elapsing between the last injection and the occurrence of purpuric/

purpuric symptoms is about four days, the shortest period being apparently a few seconds, and the longest being fifty-eight days. In one case, (the first of the series) no time is stated, in two cases, a few days is the time given. In not a few cases, the patients left hospital after their arsenical injection feeling well, only to return a few hours or days later with well marked clinical signs of purpura.

(6) Haemorrhage.

The extent and the degree of the haemorrhage varies. Most frequently it takes the form of spontaneous extravasation of blood into the skin, petechial spots, nose bleeding, and bleeding from the gums. Haemorrhage from the vagina, rectum and bladder appears to be less common. The amount of haemorrhage appears to depend upon the degree of thrombocytopenia present, but there are certain exceptions to this generalisation.

The following table shows that the relationship between the haemorrhage and the number of circulating blood platelets is not always a constant factor.

TABLE III./

TABLE III.

Case No.	Degree of haemorrhage.	Platelet Count.
2	Moderate	Nil
7	Severe	175,000
12	Severe	18,000
18	Moderate	Nil
19	Moderate	Nil

It would seem, therefore, that apart from any effect caused by a diminution in the number of platelets, some other factor may play a part in the degree of haemorrhage, such as, the extent of damage to the endothelium of the vessel wall, or some interference with the normal blood coagulation complex.

In the literature reviewed, references to post-mortem findings are very scanty, and details as to the extent and severity of the haemorrhage have been seldom recorded.

Buist (1925) found post-mortem, haemorrhage into the skin, lips, wall of the left ventricle, mesenteries, great omentum and large intestine, with bleeding into both kidneys, and petechial haemorrhages at the base of the brain.

Bocage and Le Filliol (1929) found post-mortem a large haemorrhage into the intestine, and purpuric spots over the surfaces of the heart, with larger haemorrhagic areas/

areas near the orifice of the tricuspid valve. Haemorrhage therefore is not confined to any particular region but may be present in any organ or take place from any part of the mucous membrane.

(7) Haematological Findings.

(1) Haemoglobin and Differential Blood cell count.

The Hb. percentage is given in twenty-two out of the thirty-six cases reported upon.
In eight of these twenty-two cases the Hb. percentage was found to be under 65.
In one case (the first of the series) the percentage of haemoglobin was not actually recorded, but as the red cell count was found to be below two million it may be taken for granted that the Hb. percentage was below 65.
It follows that only about 40 per cent of the recorded cases show a marked degree of anaemia.
A slight degree of anaemia is present in only 13.5 per cent of cases.
A marked diminution in the number of red cells is present in these cases which proved fatal, the average red cell count being 2,537,000 per c.cm. as compared with 4,230,000 per c.cm. in those cases which recovered.

(2) A study of the white cell content of the blood was made in 25 cases.

Leucopenia was present in 9 cases.

Of/

Of these nine cases, three recovered, and six died. In those cases which recovered, in one instance the blood showed the presence of a monocytosis, and in another a granulocytopenia.

The average white cell count in these three cases was 3966 cells per c.mm, and the percentage of polymorphonuclear cells was 47.

Of the six cases which died, five showed agranulocytopenia, accompanied by a lymphocytosis in four instances. The sixth case showed an absolute agranulocytosis and a lymphocytosis.

The average white cell count in these six cases was 2225 cells per c.mm., with an average of 15 per cent polymorphonuclear cells.

The conclusions to be drawn from the data obtained from these blood examinations may be summarised as follows:-

(1) A severe degree of secondary anaemia is not always present in cases of post arsphenamine purpura. Anaemia to some extent is present in about 50 per cent of cases.

(2) The presence of granulocytopenia is a grave omen, and the prognosis would appear to depend upon the degree of granulocytopenia present.

(3) In many cases of post-arsphenamine purpura, the bone marrow escapes damage, and in these cases the prognosis is on the whole good.

(4)/

(4) Examination of the blood is essential from the prognostic point of view, and this should be carried out immediately any sign of purpura is apparent.

(8) The Platelets

It is still a matter of doubt as to the actual part played by the blood platelets in purpura haemorrhagica, and although thrombocytopenia frequently accompanies purpura haemorrhagica some writers do not admit that this is of any clinical or pathological significance. It would appear that under normal conditions of health, the numerical range of the platelet count varies to a considerable extent. MacKay (1931) states that the normal numerical limit may be anything between 250,000 and 450,000.

Dameshek (1932) gives the normal limit as between 500,000 and 900,000. As we are mainly concerned with the significance of a low blood platelet count, any figure below 250,000 per c.cm. will be taken to indicate that thrombocytopenia exists.

Most observers agree that there is a decrease in the platelet count in post arsphenamine purpura. From a study of the cases examined this view appears to be correct.

It/

It will be noted that an examination of the blood platelets was made in twenty-seven patients out of the total number of thirty-six.

In two cases the number of blood platelets was stated to be "normal".

In one case "very few" were observed and in three cases the platelet count was "low". In fifteen cases the blood platelets were decreased, and in six cases absent altogether. Thrombocytopenia was therefore present in twenty-five out of the twenty-seven cases, that is in 92.5 per cent of cases.

Actual figures of the platelet count are given in twenty-two cases, and the average count works out at 65,445 platelets per c.mm. per patient.
Five deaths occurred in cases showing thrombocytopenia. Of these, only two patients showed complete absence of platelets. The average platelet count in the other three cases was 121,000 platelets per c.mm.
In the patients who survived the complication, the average platelet count was 63,223 per c.mm. per patient.

From these figures one might conclude that whilst the thrombocytopenia almost invariably accompanies post arsphenamine purpura the number of platelets in the circulating blood does not appear to have a direct bearing upon the prognosis of this complication.

Zunz/

Zunz and Vesselovsky (1934) in their experiments on the rabbit noted a diminution in the number of platelets in the carotid blood five to ten minutes after the intravenous injection of 0.1 to 0.2 gm. neoarsphenamine or sulpharsphenamine.

Jui-Wu-Mu (1929) states that the platelets show at first a fall in from ten to thirty minutes and then a rapid rise, after the intravenous injection of neo-arsphenamine. In a study of fourteen cases he found a fall in the number of platelets in ten cases, the platelets then numbering 170,000 to 300,000 per c.cm. and no patient developed purpura haemorrhagica. The platelet count was normal six hours later.

W.R. Kennedy (1928) states that it is a common observation that haemorrhagic lesions develop where the blood platelet count is below 60,000. This author states that haemorrhage occurs when the toxic influence of the arsenic is exerted upon the blood platelets, giving rise to a symptomatic purpura haemorrhagica i.e. Group II, in contrast to Group I where he states "there is no bleeding from the mucous membrane - i.e. a non-thrombocytopenic purpura."

But haemorrhage can, and does occur in the absence of thrombocytopenia. Thrombocytopenia cannot therefore be regarded as a sine qua non in relation to haemorrhage.

In my own series of six cases, the platelet count in/

in two instances was within normal range and yet haemorrhage occurred and in the case reported by Hudson (1935), the blood film showed an absence of platelets three days after the cessation of haemorrhage.

Scarborough and Stewart (1938) have reported one case in which the platelets numbered 500,000 with the presence of epistaxis, haematemesis and extensive petechial haemorrhages.

MacKay states that it is very doubtful if the thrombocytopenia is the cause of the characteristic lesions in purpura haemorrhagica and that the platelet diminution is merely a superimposed phenomenon. This writer's researches also led him to conclude that the most important factor in controlling spontaneous capillary haemorrhage or duration of bleeding time is not the number of platelets in the circulation, but the ability of the vessel wall to contract. MacKay conaiders that the haemorrhages in purpura haemorrhagica are due to a defect in the capillary wall.

Tidy (1928) suggests that so long as the endothelium remains intact no haemorrhage will occur even in the absence of platelets, but when damaged, then the deciding factor will be the number of platelets available for protection of the endothelium.

Bedson (1922) whose work has already been quoted, concluded that the main factors concerned in haemorrhage were/

were a toxic action on the endothelium of the vessels, and the removal of platelets from the circulation.

The foregoing evidence is sufficient to indicate that the absence or reduction of platelets in the circulation is not the sole factor leading to purpura haemorrhagica.

In considering the question of thrombocytopenia it would be expedient to refer now to the investigations carried out by certain workers as to the cause of the decrease in the number of platelets.

In thrombocytopenic purpura of unknown origin, it is recognised that removal of the spleen is frequently followed by a great improvement in the condition. In view of this, certain workers have set out to establish the presence of a platelet reducing agent in the spleen.

in 1938 Troland and Lee reported the presence of a platelet reducing principle in acetone extracts of spleens from patients suffering from thrombopenic purpura; when given intravenously to rabbits, these extracts lowered the count of the circulating platelets.

Several workers have attempted to confirm these findings by Troland and Lee.

Major and Weber (1939) failed to obtain similar results with splenic extracts from two cases of thrombopenic purpura.

Watson (1941) after a series of experiments with splenic/

splenic extracts from three cases of thrombopenic purpura injected into rats and rabbits, failed to find any evidence to substantiate the existence of a specific thrombopenic factor.

Hobson and Witts (1940) however obtained a fall in the number of platelets in the rabbit with an acetone extract of the spleen from a case of thrombopenic purpura.

It appears from a study of the literature that a fall of platelets can occur in the rabbit when spleen extracts are administered intravenously, but the effect is inconstant, and results obtained in these investigations are conflicting.

Arsenobenzol Compounds in relation to the Blood Coagulating Mechanism.

The process of normal coagulation is still imperfectly understood.

Of the current theories that of Howell is the one most generally accepted. The essential factor in the process is the conversion of soluble Fibrinogen into the insoluble fibrin.

Fibrinogen is a type of protein which is formed in the liver. It is well known that the Arsphenamines are capable of seriously interfering with the function of the liver cells, and it may be that the haemorrhage is/

is due to the destructive action of the arsphenamine upon the fibrinogen or perhaps to a lack of production of fibrinogen as a result of liver cell damage.

Flandin and Tzanck (1921) appear to have been the first to make known the anticoagulative action upon the blood of the arsenobenzols, both in vitro and in vivo. These authors state that in vitro, if the blood is collected in a glass vessel, the sides of which have been moistened with a weak solution of arsenobenzol solution it will remain incoaguable indefinitely, in vivo, when the blood is taken from an individual who has received an intravenous injection of an arsenobenzol, it will be observed, that the coagulation of the blood is delayed, and that this delay will last from 30 minutes to 24 hours or longer. If further samples of blood are taken, incoagulability continues for a period varying from a few hours to several days, the phenomenon then gradually passes off.

Flandin and Tzanck also state that the anti-coagulating action does not appear to depend upon the quantity of the drug injected, but the action appeared to be more sustained in those patients who had received a great number of injections in a series.

According to these authors the anti-coagulating effect is due entirely to the arsenobenzol, and has nothing to do with the syphilitic toxin. They state that the arsenobenzols do not seem to act on the blood corpuscles/

corpuscles or platelets of the blood which are not modified in form or number.

Anwyl-Davies and Mellanby (1923) found that the addition of one part of arsenobenzol to a thousand parts of blood prevents the coagulation of blood in vitro, and that therapeutic doses, used in clinical cases, have practically no effect on blood coagulation except to a small degree after long courses of administration.

According to these authors, the experiments in vitro indicated that the anticoagulant effect of arsenobenzol was exerted on the last phase in blood coagulation i.e. on the action of thrombin on fibrinogen. As a result of their experiments they conclude that the combination of the arsenobenzol with fibrinogen depends upon the organic grouping, since arsenious oxide has no effect on the coagulability of the blood, nor does arsenobenzol combined with glucose (stabilarsan) alter the blood coagulation. In their clinical observations they found that therapeutic doses of the various Salvarsan preparations intravenously injected into men or women have practically no effect on the coagulability of the blood.

As a result of these investigations it may be concluded that the administration of arsenobenzol compounds over a prolonged period of time tend to have a/

a slight anticoagulative action upon the blood. These compounds used in normal therapeutic doses may be said to have a negligible effect in the aetiology of post-arsphenamine purpura.

Capillary Fragility in relation to Post-arsphenamine Haemorrhagica.

Bell, Lazarus and Munro (1940) studied the effects of the ingestion of vitamin C in capillary fragility.

The fragility of the capillaries of the skin of the anti-cubital fossa was examined by Gothlin's method.

Large doses of vitamin C were given to thirty-five subjects after their capillary fragility has been estimated. The capillary fragility was estimated fourteen days later. Of twenty-one cases with original values of eight or more petechiae the vitamin treatment was followed by a reduction to the values of eight or under in sixteen cases.

In fourteen cases showing originally less than eight petechiae vitamin C had no effect on the number of petechiae.

In their series of 346 cases these authors found five subjects with an initial count above eight, and no response to the first treatment with ascorbic acid, were found to resist a further ten days course of 200 mg. of vitamin C daily.

These five subjects were given large doses of vitamin/

vitamin P (Hesperidin) without producing any change in the capillary fragility.

These authors conclude from their investigations that:-

(1) when the petechial count was eight or over, the ingestion of vitamin C reduced the petechial count to less than eight in two weeks.

(2) The ingestion of vitamin C has no effect on petechial counts below eight.

(3) There are a few healthy persons (five in 346) with increased capillary fragility which is not influenced by the administration of vitamin C or vitamin P.

(4) Apart from abnormal influences, e.g. fever, and the administration of heavy metals, two factors influence capillary fragility in normal health: menstruation, and ascorbic acid.
They also conclude that their investigations lead to the suggestion that other factors are involved.

Scarborough and Stewart (1938) in their experiments showed the value of vitamin P (hesperidin) in the treatment of purpura occurring as a toxic manifestation of antisyphilitic therapy with arsenic. They found that the subjects examined had a low capillary resistance, and that this was raised by the administration of vitamin P.

Horne and Scarborough (1940) believe that vitamin

P/

P is a factor in increasing the capillary resistance and publish the result obtained in the case of purpuric haemorrhagica following arsenobenzol treatment. After the administration of vitamin P, clinical improvement was noted and no further petechial haemorrhages developed.

Scarborough (1940) as a result of his studies in deficiency of vitamin C and vitamin P in man states that a low capillary resistance in people with various forms of nutritional deficiency was found to be associated with a deficiency of vitamin P. This author points out that it is possible that some forms of purpura may have a nutritional basis.

SECTION IV. CONCLUSIONS FROM CASES REVIEWED.

From a study of the foregoing thirty-six cases, together with literature relevant to this subject, it may be concluded that:-

(1) Post-arsphenamine purpura is a comparatively rare complication in the treatment of syphilis.

(2) In the absence of accurate knowledge as to the aetiology of the condition, the present classification can only be provisional. This would appear to be due to an endeavour on the part of some observers to establish post-arsphenamine purpura/

purpura as a clinical entity, whilst others regard it merely as a part of a more complex disease.

(3) The Drug. In the cases reviewed Neoarsphenamine was the drug chiefly responsible but this is probably because of its more frequent use, and if sulpharsphenamine had been used to a similar extent more reactions with the latter drug would have occurred. It is not possible, however, to state definitely which drug is most frequently associated with post-arsphenamine purpura.

(4) The number of injections, the particular dose, or the total amount of the drug given, do not appear to be important factors in the aetiology. The complication,however, generally occurs after several injections of arsenic have been given, the patient apparently developing a sensitivity to the drug.

(5) Prodromal symptoms are frequent and were present in 61 per cent of the cases reviewed.

(6) Thrombocytopenia is not the primary cause of the complication. Post-arsphenamine purpura may occur in the absence of thrombocytopenia.

(7) In those cases where there is a marked diminution in the thrombocyte count, the haemorrhage tends to be more severe.

(8)/

(8) Therapeutic doses of arsenobenzol compounds do not have any significant anticoagulative action on the blood.

(9) A deficiency of vitamin "P" and "C" has been found associated with a low capillary resistance in cases of post-arsphenamine purpura. It has been suggested that a vitamin deficiency may be a responsible factor in some cases of purpura.

PART II.

SECTION I. Technique Employed.

II. Report on cases .

III. Discussion.

IV. Conclusions.

SECTION I. TECHNIQUE EMPLOYED.

BLOOD EXAMINATION.

Enumeration of the red and white blood cells was done by means of the Thoma haemacytometer. Hayens solution was used in the case of the red cells, and the diluting fluid for the leucocytes consisted of 1 cc. glacial acetic acid in 100 cc. of distilled water, to which methyl green was added.

The haemoglobin estimations were carried out by means of a Sahli haemoglobinometer.

The stain used for the Differential Count of the white cells was Jenner-Giemsa.

Enumeration of Blood Platelets and reticulocytes was performed according to the method suggested by William Dameshek (1932). The diluting fluid consisted of a 3.5 per cent sodium citrate with sufficient brilliant cresyl blue stain added to give the solution a bright blue colour.

The bleeding time was estimated according to Duke's method, and Lee & White's method was adopted in the estimation of the coagulation time.

A mercurial Baumanometer was used for the Blood pressure readings. Smears and cultures were examined and reported upon by the Clinical Bacteriologists to the Venereal Disease Department at the Royal Infirmary Edinburgh.

The/

The capillary resistance was determined by a positive pressure Technique. The arm cuff was applied to the upper arm and the pressure was quickly raised to 100 mm. Hg. and maintained for five minutes. At the end of this time the number of petechiae on the whole arm below the cuff were counted.

SECTION II.

CASE I. A female aged twenty-four, married, with one child eleven months old. She looked a healthy person, and weighed 8 st. 8 lbs.

The patient reported to the clinic on the 2nd February 1932 and she had suffered from genital sores for two months previous to reporting at the clinic.

The Blood Wassermann test was strong positive.

On examination the patient was found to suffer from numerous condylomata around the anus and on the labia.

The inguinal glands in both groins were enlarged.

The tonsils were enlarged and there was some congestion of the throat present, with a mucous patch on the right tonsil.

Treatment.

2.2.32 until 5.5.32. 12 weekly injections of 0.3 gm. Neo Kharsivan. At the end of this series of injections the patient complained of dizziness and pain behind both ears.

6.6.32 until 5.10.32. 15 injections (mostly given at weekly intervals) of 0.3 gm. Bismuth (Hyboloid B.W.) At the end of this period the blood Wassermann test was negative.

5.12.32 until 15.3.33. 10 injections at periods varying from seven to fourteen days. The first of these injections was 0.15 gm. Kharsulphan, the second was 0.15 gm. Neokharsivan, and the rest were 0.3 gm doses Kharsulphan.

After the second dose in this series, that is after the 0.15 gm. Neokharsivan the patient complained of sickness immediately after the injection. It was noted that the patient had lost 4½ lbs in weight since beginning treatment.

From 20.3.33 until 14.8.33. 15 injections of Bismuth totalling 4.35 gms.

From 7.10.33 until 25.11.33 patient received

1 injection of 0.15 gm. Kharsulphan

and 4 injections of 0.3 gm. Kharsulphan.

History.

On 2.12.33 the patient reported at the clinic and stated that she had bleeding from the gums. This had occurred about two hours after each of the last two injections, but she had not mentioned it at the clinic. On being questioned the patient admitted that a similar bleeding had occurred a *** year previously.

Examination.

On examination purpuric patches were observed on both arms and legs. These were for the most part on the flexor aspect of the forearms and on the front of both thighs. These varied in size, some were only petechial spots whilst others were the size of a shilling. A very large purpuric patch 3½ inches in diameter was present over the left biceps muscle. The gums were spongy and inflamed, with pus oozing from some septic roots of teeth present.

There/

BLOOD EXAMINATION. CASE NO. 1.

Hb.	Red Cells	White Cells	Poly-Morphs	Lympho-cytes.	Eosino-phils.	Mono-cytes.	Reticulo-cytes.	Plate-lets.	Bleeding Time.	Coag. Time.	Capillary Resistance.
68%	3,520,000	5,800	78%	20%	1%	1%	1%	200,000	4	5½	Positive

There was a moderate amount of bleeding from the gums, starting in the lower jaw, the breath was foetid, and the throat was congested and the tonsils enlarged.

Circulatory System. The heart sounds were normal. There was no cardiac enlargement. Blood Pressure 120/68. The pulse and temperature were quite normal.

Abdomen. Examination of the abdomen was negative.

Nervous System. No abnormality detected.

Urinary System. The urine was normal, no trace of albumin had ever been present throughout the treatment.

A blood examination was done on the 2.12.33 the result of which is given.

(See Table)

Capillary Resistance. A tourniquet applied for five minutes at 100 mm. Hg. pressure, produced numerous small petechiae showing the presence of an increased fragility of the capillary walls.

Bacteriological Examination.

A culture was prepared from pus taken from the gums, this showed a non-haemolytic streptococcal growth, and staphylococcus albus. A smear was also examined and this showed numerous fusiform bacilli, a few spirochaetes and gram positive cocci.

Treatment.

This patient refused to remain in hospital for further observation but she was given calcium chloride

by/

by the mouth (gr. XV thrice daily). She made a complete recovery, and no further arsenic was administered.

SUMMARY OF CASE.

Total arsenic given over period of twenty-two months 7.2 gms.

Nature of arsenical preparation 3.6 gms Kharsulphan and 3.6 gms. Neokharsivan.

Patient had marked symptoms of intolerance prior to onset of purpura.

Mild thrombocytopenia present.

Bleeding time slightly increased.

A toxic focus of infection was found present in the teeth and gums, at the time of the onset of purpuric symptoms.

CASE 2. The patient was a female aged 55, unmarried. Her weight was 6 st. 2 lbs.

In March 1932 the patient was sent to The Royal Infirmary Edinburgh by her doctor because of a swelling on the lower lip of two months duration.

The blood Wassermann test was found to be strongly positive.

Antisyphilitic treatment was started on 29.3.32.

From 29.3.32 until 21.7.32. 13 weekly injections of Kharsulphan were given, all were 0.3 gm. doses except the first which was 0.15 gm. During this period fourteen weekly injections of 0.3 gm. Bismuth (Hypoloid B. W. & Co.) were also given.

After this the patient had no further injections for a period of two months.

From 12.9.32 until 17.11.32. 10 weekly injections of Kharsulphan were given, all doses were 0.3 gm. except the first which was 0.15 gm.

The blood Wassermann test was now negative.

From 12.1.33 until 20.4.33. 15 weekly injections of 0.3 gm. Bismuth (Hypoloid were given. The patient at this period of her treatment felt very well and had gained 3 lbs in weight.

From 15.6.33 until 6.7.33. 5 weekly injections of Kharsulphan were given, all 0.3 gm. doses except the first which was 0.15 gm.

On 10.7.33, that is three days after the last injection of Kharsulphan the patient reported at the clinic, with marked purpuric haemorrhages. On being questioned the patient stated that she had vomited clots of blood and passed blood from the bowel the day following her last injection of Kharsulphan. She was admitted to hospital and given Calcium Lactate gr. XV every four hours.

Examination.

This revealed purpuric haemorrhages on the buttocks and legs. The largest of these was about the size of a half crown, and the haemorrhages were more marked on the flexor aspects of the legs.

There was no bleeding from the gums. There were several decayed/

BLOOD EXAMINATION. CASE No. 2.

Hb.	Red Cells	White Cells	Poly-Morphs	Lympho-cytes.	Eosino-phils.	Mono-cytes.	Reticulo-cytes.	Plate-lets.	Bleeding Time.	Coag. Time.	Capillary Resistance
27%	1,590,000	3,600	30%	65%	3%	2%	2%	NIL	15	7½	Positive

decayed teeth present, but the mouth was not in a septic condition. The tonsils were enlarged, and somewhat congested, and some thin pus could be expressed from both tonsils. The patient admitted that she had frequently suffered from "sore throat".

The pulse, temperature and respiration were all normal.

Circulation. (1) There was no history of rheumatism or other illness to account for the presence of the valvular lesion. ?

(2) There were no symptoms of cardiac involvement.

(3) The Blood pressure reading was systolic 160, diastolic 88.

(4) Over the apex a distinct presystolic murmur was audible.

Abdomen. The spleen was not palpably enlarged, and no abnormality could be found in the abdomen.

Nervous System. No abnormality.

Urinary System. No abnormality.

On 11.7.33 the patient passed a considerable amount of blood in the urine and conjunctival haemorrhages were present. She looked pale and she was suffering from shock. The pulse rate was 120, temperature 96.8, and the respirations rapid. A blood transfusion was given at 6 p.m. and the patient almost immediately looked better.

A blood examination was done on admission.

(See Table)

On 12.7.33 an enema was given, and the patient passed a large quantity of dark brownish red blood in the stool. No fresh external haemorrhages had occurred, and the pulse was satisfactory. During the afternoon the patient vomited a little dark brown blood.
At 6 p.m. the patient was again transfused with one pint of blood. The pulse rate rose to 112, and the temperature to 100.6 at 7 p.m. At 7.30 p.m. she was given 1/3 gr. omnopon, and thereafter passed a comfortable night.
On 13.7.33 the patient seemed better, a large haematoma had developed at the site of the hypodermic injection. The temperature was 99.2°F. and the pulse rate 104. Blood was still present in the urine and faeces.
On 14.7.33. Very little change was noted.
The pulse rate however increased, and the temperature was 100°F. There was some diarrhoea and the stool contained blood. In the evening the abdomen was much distended. The pulse remained fast, the patient looked very pale and her respirations were laboured and rapid. At 9 p.m. she was transfused with 1 pint of blood and 5 cc. pernaemon.
On 15.7.33. The patient appeared to have improved again, the pulse rate was 96 and temperature 97.6°F. The respirations were easier and normal in rate. Blood was still present in urine and faeces.

On/

On 16.7.33. A large quantity of blood was passed per rectum, and the urine also contained blood. The patient was much weaker. She became progressively worse, the pulse was very feeble, and the patient was sick and vomiting. A further blood transfusion and 5 cc. pernaemon was given. This time however the response was not so marked. The patient was then given a rectal lavage, followed by a starch and opium enema.

17.7.33. An improvement was again noted in the patient's condition. The pulse was full and strong and the temperature and respirations were normal.
A further colon lavage was given and thereafter a starch and opium enema. A very large quantity of blood was returned.
5 cc. pernaemon was given along with a transfusion of blood at 7.30 p.m.

19.7.33. The patient was fairly comfortable, pulse good and the temperature was normal. The urine was practically clear of blood, only a few red blood cells were found in a centrifuged deposit. The abdomen however was very much distended, and the patient was frequently sick. She was unable to take any fluids by the mouth.
A starch and opium enema was given, and again a great quantity of blood was returned.
5 cc. pernaemon was given and also 0.5 cc. pituitrin at 8 p.m. The patient became much distressed at

9.30/

9.30 p.m. and a further 0.5 cc. pituitrin was given. 1/6 omnopon was also given. The patient however failed to respond. She vomited frequently, gradually became comatose, and died at 5.55 a.m on the 20.7.33.

Post-mortem Findings. No obvious oedema present. A marked purpuric rash was present on the lower limbs.

Respiratory System. The lungs were emphysematous, and in addition they showed a certain amount of terminal oedema.

Circulatory System. Externally, the heart showed one or two tiny subepicardial haemorrhages over the coronary sinus posteriorly. The myocardium throughout the heart was thin, pale and friable. Subendocardial haemorrhages were present in the wall of the left ventricle, and in the papillary muscles.

Alimentary System. A good deal of altered blood was present in the lumen of the large gut. No definite bleeding point was detected anywhere in the alimentary tract, the blood evidently being the result of a general capillary oozing. The liver showed a moderate degree of chronic venous congestion.

Genito Urinary System. There was no evidence of chronic kidney disease. The right kidney near the upper pole was the site of a number of small haemorrhages in the cortex. The pelves showed a good deal of submucous haemorrhage.

Haemopoietic System. Bone marrow from shaft of the femur showed only very slight indication of reaction. The microscopic examination showed a very strong erythroblastic reaction. Nucleated reds were present in all stages from stem cell downwards, the majority being in the normoblastic stage. A moderate leucoblastic activity was in progress.

There was a large number of megakaryocytes both degenerating and in the process of formation. These cells were present in greater numbers than they would have been in pernicious anaemia.

The spleen was rather large, moderately soft in consistence and of a bright red colour.

Connective Tissue. The retroperitoneal areolar tissue throughout the abdomen showed numerous small areas of haemorrhage.

SUMMARY OF CASE.

Total amount of arsenic given over a period of sixteen months was 7.95 gms.

Nature of arsenical preparation - Kharsulphan only.

No indication of intolerance to arsenical therapy before the sudden onset of symptoms.

History of frequent sore throat. The tonsils were the seat of toxic infection.

Complete absence of platelets.

Bleeding time markedly prolonged.

Coagulation/

Coagulation time slightly prolonged.
Transfused with one pint of blood five times in seven days.
Improvement in patient's clinical condition after each transfusion.

CASE 3. This was a female patient aged 34, married, with two children.
She was very obese weighing 15 st. 2 lbs. Her menstrual periods had always been scanty and irregular, occurring every ten weeks.
After the birth of her second child in 1929, she developed puerperal fever, and at this time she had a large septic sore near the anus, which burst, with a profuse discharge of pus.
She reported atthe Skin Department of the Royal Infirmary in July 1932, and sought advice on account of redness and irritation in the region of the urethra.
A large tertiary cutaneous lesion was present on the face, spreading over both cheeks and forehead.
The Wassermann test was found to be strong positive.

Treatment. On 13.7.32 The patient received her first injection of 0.15 gm. Neokharsivan and on the 25.7.32 she received 0.3 gm. Neokharsivan.
From 1.8.32 until 31.10.32, 10 weekly injections of Kharsulphan were given, all being 0.3 gm. doses except the first which was 0.15 gm.

13 weekly injections of 0.3 gm. Bismuth (Hypoloid) was also given during the same period. The patient complained of dizziness after the 5th dose of Kharsulphan, but the dose of the drug was not reduced.

From 23.1.33 until 15.5.33. 11 injections of Kharsulphan were given at somewhat irregular periods owing to teeth extraction. One of these was given after an interval of twenty-eight days, three others were given at fortnightly intervals, all were 0.3 gm. doses except the first which was 0.15 gm.

From 7.8.33 until 20.11.33. 15 injections of Bismuth Hypoloid) all 0.3 gm. doses except the first, this being 0.15 gm.

The Wassermann reaction was now weak positive.

From 8.1.34 until 22.1.34. 3 weekly injections of Kharsulphan, first one being 0.15 gm. dose, the others being 0.3 gm. doses.

The patient reported to hospital on the 5.2.34, complaining of bruises on her arms and buttocks. She said that about two hours after her injection on the 15.1.34, she saw small red spots round the neck, and on the right arm, after she went home; in the afternoon she felt shivery and became feverish at night. She also stated that half an hour after her injection on 22.1.34 she had experienced a shivering, with severe headache, and pain in the back.

Examination./

Examination 5.2.34. The patient looked anaemic and she had greyish unhealthy pallor. She was very obese and suffered from dyspnoea. Her temperature was normal, the pulse rate 96, respirations were normal. There was some tenderness over the frontal sinuses, especially on the left side. Small purpuric spots varying in size from one to five millimetres in diameter were presemt on the neck, chest and left arm, and large purple bruises were present on the left wrist, and over the left buttock. There were a few fresh purpuric haemorrhages present over the flexor aspects of the lower limbs.

The throat was red and congested. The tonsils had been removed some years previously but pus could be expressed from the tonsillar region. A throat swab was taken and this showed haemolytic and non-haemolytic streptococci (the latter predominant).

Staphylococcus albus and coliform bacilli present on culture.

There was no bleeding from the gums or other mucous membranes.

No blood present in urine or faeces.

Circulatory System. The Blood pressure reading was systolic 140, diastolic 72. The heart borders could not be defined owing to the patient's obesity.

The heart sounds were of a slapping nature indicating early/

BLOOD EXAMINATION. CASE 3.

Hb.	Red Cells	White Cells	Poly-Morphs	Lympho-cytes.	Eosino-phils.	Mono-cytes.	Reticulo-cytes.	Plate-lets.	Bleeding Time.	Coag. Time.	Capillary Resistance
60%	4,500,000	8,740	72%	25%	1%	2%	.9%	300,000	3 mins.	4 mins.	Neg.

early myocardial damage but no valvular leakage could be detected.

Nervous System. No abnormality.

Abdomen. Nil to palpation.

The urine was perfectly normal.

The patient had not lost any appreciable weight during her treatment.

(See Table)

This patient was allowed to go home, as she resented hospitalisation. She returned on 14.2 .34, and apart from a few fresh petechial haemorrhages on the neck, her general condition had improved. She made a spontaneous recovery.

SUMMARY OF CASE.

A mild case of purpuric haemorrhage with no reduction in the number of platelets.

Total amount and nature of arsenic given over a period of eighteen months

Neokharsivan	0.45 gms.
Kharsulphan	6.75 gms.

Premonitory symptoms were present in the form of giddiness, shivering, headache and haemorrhagic spots.

The patient suffered from sore throat for ten days prior to the onset of her symptoms. A focus of infection was found to be present in the throat.

There was no abnormality present in the blood.

The blood platelets were not reduced in number.

CASE 4. The patient was a male aged 29. He weighed 8st.9½lbs. He reported to the Royal Infirmary on 4.7.33, and he was found to be suffering from gross oedema of the prepuce and a purulent sub-preputial discharge.

On 7.7.33 spirochaete Pallida were found present in the discharge. There was enlargement of the inguinal glands on the right side. Otherwise the patient appeared to be well.

Treatment. From 11.7.33 until 29.9.33 the patient was given nine injections of Neokharsivan, all were 0.45 gm. doses except the first and the last which were 0.3 gm. doses. During this period he received 3.6 gms. Bismuth (hypoloid).

From the 3.11.33 until 24.11.33, three injections of neokharsivan were given, each dose being 0.45 gms. During this time four injections of 0.3 gm. Bismuth were given.

On 26.11.33, that is, two days after his last injection of Neokharsivan, when blowing his nose it started to bleed. It continued to bleed all night fairly profusely. The following evening the patient noticed "red spots" on his legs.

He was admitted to hospital on 29.11.33.

Examination. The patient was very thin, and undersized. He was pale but not markedly so. His pulse rate/

rate was 88. Temperature subnormal and respirations normal. There was a widespread purpura eruption on the upper part of the front of the chest, and over the shoulders. There were a few diffusely scattered spots on the thighs and legs. Their size varied from one to three millimetres in diameter. There was considerable oozing of blood from the nose and mouth. Haemorrhagic blebs could be seen on either side of the nasal septum. These were also present inside the mouth, at the sides of the tongue, inside the lips, and also on the surface of the tonsils. There was also some oozing round the roots of the lower teeth. The tonsils were difficult to demonstrate, these being submerged, but a small amount of pus was expressed from the left tonsil. The tonsillar glands on both sides of the neck were swollen. The upper teeth were artificial while the lower teeth were septic, the gums were red and painful to touch - they bled easily. The tongue was coated and furred. Cultures from the gums showed a growth of diphtheroid bacilli and non-haemolytic streptococci. Cultures made from the tonsillar section showed staphylococcus albus and a good growth of non-haemolytic streptococci.

Cardio-vascular system. The blood pressure reading was 130/68. The pulse was regular, and of low tension. The heart was not enlarged, and the heart sounds were pure.

Nervous/

BLOOD EXAMINATION. CASE 4.

Hb.	Red Cells	White Cells	Poly-morphs.	Lympho-cytes.	Eosino-phils.	Mono-cytes.	Reticulo-cytes.	Plate-lets.	Bleeding Time.	Coag. Time	Capillary Resistanc
62	3,410,000	12,400	75	25	22	3%	.9	25,000	12 Mins.	4½	Positive

Nervous System. There was no abnormality discovered in the nervous system.

Abdomen. Spleen was palpable just in front of the anterior axillary line. The liver was not enlarged and there was no evidence of any other abdominal derangement.

Respiratory System. The chest was thin and there was a slight tendency to pigeon chest. The respiratory excursion was poor. Slight dullness was present over the upper left lobe in front. Over the right upper lobe the breath sounds were vesicular with median crepitations and rhonchi. Over the upper left lobe there was medium pitched bronchial breathing with rhonchi and over the left apex fine crepitations were present.

Urinary System. The urine was normal in every respect.

Blood Examination. (see Table)

This patient was transfused with 12 ozs. of blood on 30.11.33, and on that date a splenectomy was performed. He had a further transfusion on 1.12.43 of 14 ozs. of blood. He made a satisfactory recovery and he was discharged on 16.12.33 to continue his treatment as an out-patient.

SUMMARY/

SUMMARY OF CASE.

The patient received 5.2 gms. Neokharsivan over a period of four months.

The onset of symptoms occurred two days after his last injection.

At the time of the onset of symptoms a focus of toxic infection was present in the teeth and gums.

The spleen was slightly enlarged.

Splenectomy was performed, and he made a very satisfactory recovery.

In March 1934 this patient was discovered to be suffering from Pulmonary Tuberculosis. Tubercle Bacilli were present in the sputum. He was then transferred to a hospital for the treatment of tuberculosis.

CASE 5. The patient was a female aged 43. Her weight was 7 stones 1 lb. She was reported to have been a healthy child. As an adult her health had been on the whole satisfactory. Her periods were regular and normal. Apart from occasional sore throats, she was not subject to minor ailments.

The lower teeth had been extracted three years previously because of pyorrhoea.

The patient reported to hospital on 27.7.33 with numerous gummatous ulcers around, and under the right knee.

The/

The blood Wassermann was positive, and the Gonorrhoeal Fixation Test gave a weak positive result.

Treatment.

31.7.33 until 23.11.33. 16 injections of Neokharsivan were given, at more or less weekly intervals, in one instance there was a lapse of three weeks, and the last three injections were given within a period of eight days. The entire series of injections were made up as follows:

8 doses of 0.15 gm. each.
4 " " 0.2 gm. "
4 " " 0.3 gm. "

After the eleventh injection of the series a trace of albumin appeared in the urine. This disappeared the next day and the urine remained free from albumin during the whole of the patient's treatment.
After the second injection of 0.15 gm. Neokharsivan, the patient stated that her left eye had become swollen and inflamed, on the evening of the injection. On the following day the eye was quite normal. Otherwise there was no untoward effect, and the patient had gained 7 lbs. by the end of her course of treatment.
13 intramuscular injections of Bismuth (Hypoloid B.W.) were given over the same period of time - each dose being 0.3 gm.

From/

From 21.12.33 until 5.4.34 the patient received fifteen weekly doses of 0.3 gm. Bismuth (Hypoloid).

On 10.5.34 the Wassermann test was still positive and a lumbar puncture was performed.

On 30.5.34 as the patient suffered from headache and a general malaise after this no further antisyphilitic treatment was given for a period of three weeks. Examination of the cerebro-spinal fluid yielded a normal result.

From 22.6.34 until 16.8.34 the patient received nine weekly injections of Kharsulphan, all 0.3 gm. doses except the first which was 0.15 gm. At the end of this series a boil developed on the left buttock, and she also suffered from a patch of infective dermatitis below the left knee. There was also some patches of seborrhoeic dermatitis over the chest and back. Whilst the skin condition was treated the patient received no further arsenical injections.

On 11.10.34 an injection of 0.15 gm. Kharsulphan was given, followed by four similar doses at weekly intervals. It was noted that the rash on the body and behind the knee became worse after each injection of Kharsulphan, and in view of this, arsenical treatment was stopped meanwhile.

On 25.1.35, when the patient reported to hospital she complained of a sore throat. The throat was found to be congested, and the tonsils were much enlarged and septic/

septic. There were ulcers present in the mouth. A throat swab showed a growth of nob-haemolytic streptococci and staphylococcus albus. Six weeks later his general condition was much improved. The throat and tonsils looked normal, and the skin condition was vastly improved.

From 7.3.35 until 11.7.35 15 injections of Bismuch (Hypoloid) were given in 0.3 gm. doses. On the 14.3.35 the patient again complained of sore throat.

From 28.8.35 until 17.10.35 15 biweekly injections of 1 cc. colloidal calcium were administered.

On 24.10.35 the patient received 0.075 gm. Kharsulphan, that is, ten months after her last injection of arsenic. A week later (31.10.35) 0.15 gm. Kharsulphan was given, and a further dose of 0.15 gm. Kharsulphan was given on the 7.11.35.

One hour after this third and last injection of Kharsulphan, the patient stated that she felt "queer", and that she commenced to shake. When going to bed the same evening, (12½ hours after her injection) she noticed some "red blisters" inside the lower lip. At 11 a.m. next day, (twenty-four hours after the injection) she noticed a swollen area on the back of her right hand, and the same evening other bruised and swollen areas appeared on her arms and legs. Unfortunately the patient did not report again until seven days after her injection. She was admitted to hospital/

hospital and the following evidence of haemorrhage was noted and further investigation of the condition made.

Examination. Numerous areas of haemorrhage were noted and these are summarised below:

TABLE IV.

Position of Haemorrhage.	Extent.
Posterior aspect right elbow	One inch diameter.
Dorsal aspect left wrist	½ inch diameter.
Dorsal aspect right hand	Haemorrhagic Spots one to three m.m. diameter.
Lateral aspect right leg extending from knee to ankle.	Large bruised areas ½-2 inches diameter.
Flexor aspect left leg	Petechial haemorrhages only.

The patient had not been aware of any bleeding from the nose or gums, she had not noticed any blood in the urine or stools.

She looked very pale, and complained of vague pains in her arms and legs. Her weight was now 7 stones 5 lbs, still 4 lbs heavier than when she started antisyphilitic treatment.

Her temperature was 97.4. The tongue was dry and furred, and she stated that she had suffered from constipation for several months and that she had no appetite.

The throat was much congested, and the tonsils were enlarged/

BLOOD EXAMINATION. CASE 5.

Hb.	Red Cells	White Cells	Poly-Morphs	Lympho-cytes.	Eosino-phils.	Mono-cytes.	Reticulo-cytes.	Plate-lets.	Bleeding Time.	Coag. Time.	Capillary Resistance
56%	3,010,000	13,500	28%	66%	2%	3%	1%	556,000	4%	3½	NEG.

enlarged and soft. Pus was expressed from both tonsils. The posterior pharyngeal wall was dry and congested. Red raw patches were present on the palate. A swab from the throat showed a moderate growth from haemolytic streptococci, and staphylococcus albus, with a scanty growth of diphtheroid bacilli.

Cardio-vascular system. The Blood pressure was systolic 110, and diastolic 90. The pulse rate was 92 per minute. There was a little irregularity of the pulse, and it was of poor volume. Examination of the heart revealed no enlargement, the sounds were pure, but there was evidence of myocardial damage, the irregularity of the pulse was due to extra systoles.

Respiratory system. There was no abnormality found on percussion. A few rhonchi were present at the right base.

Nervous system. No abnormality detected.

Abdomen. Normal to percussion and palpation.

Urinary system. The urine was quite normal. Only once during the treatment a trace of albumin was found to be present.

The result of the blood examination is given.

(See Table)

This/

This patient made a spontaneous and satisfactory recovery from the complication. She remained in hospital for fourteen days. During this time there was no further haemorrhages, and the haemorrhagic patches rapidly improved.

Treatment with Bismuth was resumed on 2.1.36, her blood Wassermann being still positive.

Since 2.1.36 until 24.9.42 the patient received 26.16 gms. Bismuth.

She is still attending hospital. No further arsenic has been administered and there has been no sign of any further purpuric haemorrhage.

SUMMARY OF CASE. Over a period of twenty-six months the patient received a total of 6.87 gms. arsenic.

An intolerance to arsenic had been noted early on in the treatment, in the form of an allergic reaction in the skin.

The patient was subject to sore throat, due to the unhealthy state of the tonsils, and a focus of infection was present in the tonsils.

Colloidol Calcium was administered for six weeks prior to the onset of purpuric haemorrhages.

A very small dose of Kharsulphan was sufficient to precipitate symptoms of purpura.

Blood/

Blood examination showed a leucocytosis with an increase in lymphocytes. The polymorphonuclear cells were greatly reduced (28 per cent).

A large quantity of Bismuth has been administered during the past seven years without mishap.

CASE 6. This patient was a female aged 47. Her weight was 10 stone 7 lbs. She was married and had six healthy children. Her only previous illness was a cholecystectomy performed in 1926.

She first reported at the Eye Department of the Infirmary, and it was found that she had Argyll-Robertson pupils, and an internal strabismus in the right eye. The blood Wassermann was found to be strongly positive.

The Gonococcal fixation test was negative.

Urethral smears were negative.

The cervical smears showed only pus cells - no Gonococci were present.

From 6.2.34 until 12.4.34 the patient was given nine weekly injections of arsenic as follows:-

1 Kharsulphan dose	0.15 gm.
1 Neokharsivan dose	0.15 gm.
5 Neopharsivan doses	0.3 gm. each.
1 Neopharsivan dose	0.2 gm.
1 Kharsulphan dose	0.075 gm.

During/

During this period the patient also received seven doses of 0.3 gm. Bismuth (Hypoloid).

Immediately after the sixth injection of arsenic, that is, after the fourth 0.3 gm. dose Neopharsivan, the patient vomited a little, but there were no other symptoms.

Vomiting again occurred after the next injection in the series of 0.3 gm. dose Neopharsivan. Later again after her last injection of the series, that is, 0.075 gm. doses of Kharsulphan the patient complained of nausea.

From 24.4.34 until 9.6.34 the patient received eight injections of Bismuth only, each dose being 0.3 gm.

On 14.7.34 small doses of Kharsulphan were again commenced starting with two 0.075 gm. doses, six injections of 0.15 gm. Kharsulphan were given.

The patient received her last injection of Kharsulphan on 8.9.34, and she complained of a discharging ear. Pus was observed to be oozing from the right ear, and that patient stated that this condition had been present for the past two weeks. She was therefore sent to the Ear Department for treatment.

On 15.9.34, one week after her last injection, the patient reported to the Clinic with purpuric haemorrhages. She was admitted to hospital.

Examination. The patient looked ill - her pulse rate was 100, temperature 97.2°F., and respirations normal.

She/

She was very pale. The right ear was still discharging. A swab taken from the ear showed a good growth of Staphylococcus albus, and coliform bacilli were present. On culture Staphylococcus albus, and diphtheroids were obtained.

The throat was inflamed, the tonsils were enlarged, congested, and pus could be expressed from the crypts. A swab from the tonsil showed on culture a profuse growth of streptococci viridans, and Staphylococcus albus.

Large purpuric patches, mostly about the size of a shilling, some slightly larger, were present on the flexor surfaces of both arms, and on the thighs of both legs. There was no bleeding from the mucous surfaces. It is noteworthy that the patient stated during the examination, that she noticed these spots beginning the day following her last injection - on 8.9.34.

Circulatory System. The pulse was full, and there was slight thickening of the radial and brachial arteries. The blood pressure reading was systolic 170, diastolic 100.

The left border of the heart was in the left nipple line and the apex beat was displaced downwards to the 6th interspace. A faint systolic murmur was heard over the mitral area.

Nervous/

BLOOD EXAMINATION. CASE 6.

Hb.	Red Cells	White Cells	Poly-morphs.	Lympho-cytes.	Eosino-phils.	Mono-cytes.	Reticulo-cytes.	Plate-lets.	Bleeding Time.	Coag. Time.	Capillary Resistance.
65%	3,000,000	4,200	68%	30%	1%	1%	.5%	56,000	5	3½	NEG.

Nervous System. The pupils reacted to accommodation, but failed to react to light. The margin of the right pupil was slightly irregular. In the right eye the presence of a paralytic internal strabismus was noted. The plantar reflex was flexor, the epigastric and abdominal reflexes normal. The knee jerks were absent, while the ankle, and biceps jerks were normal. Romberg's sign was negative. Sensation was unimpaired.

Abdomen. The tip of the spleen was just palpable, otherwise no abnormality was detected.

Urinary System. There were no abnormal constituents present in the urine.

The findings in the blood examination are recorded.

(See Table)

The patient had never lost weight. On 24.9.34, the patient weighed eleven stones. Two days after the appearance of the purpuric spots, a few more purpuric patches appeared on the thighs, but no bleeding from the mucous membrane occurred. Treatment consisted in the administration of Calcium Carbonate gr. XV thrice daily. The patient made an uninterrupted recovery, and she was allowed to go home on 6.10.34. She reported regularly each week, but no further symptoms of purpura were noted.

On 20.10.34 however the patient complained of a very itchy/

itchy skin, and that she could not sleep at night for the itch. The onset was quite sudden. Examination revealed a generalised patchy eruption of the trunk and legs, the rash was slightly raised, and in appearance resembled an urticaria. An injection of 0.3 gm. Theostab. was given, and repeated a week later. At the end of this time the rash had disappeared and the patient felt very comfortable. When last seen at the Clinic on 3rd Nov. 1941 she was enjoying normal health.

SUMMARY OF CASE. The total amount of arsenic given over a period of seven months amounted to 1.85 gms. Neoarsphenamine.
1.27 gms. Sulpharsphenamine.

There were unmistakable early signs of intolerance to arsenical therapy, before the onset of purpuric haemorrhages.

A comparatively small total amount of arsenic was administered and small doses were given during the second and last series of arsenical injections.

The patient was suffering from a discharging ear, and the tonsils were unhealthy at the time of the onset of symptoms.

The spleen was slightly enlarged.

The onset of symptoms occurred about twenty-four hours after the injection of arsenic.

Thrombocytopenia and anaemia were the outstanding features in the blood examination.

SECTION III.

DISCUSSION.

(1) The Disease and its stage.

(2) The Drug Employed, dosage, and duration of Treatment.

(3) The type of Individual.

(4) The onset of Symptoms.

(5) Essential Features of the Blood Examination.

(6) Suggestions as to the prevention of the Complication.

(7) Treatment of the Established condition.

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(1) THE DISEASE AND ITS STAGE.

The incidence of syphilis is reckoned to be about 5 per cent in the general population, and the manifestations of syphilis are so protean that it might be argued that the syphilis per se was the cause of the purpura.

Lovemann (1936) has drawn attention to the possibility of syphilotoxic action on the bone marrow.

I have been unable to find any record of purpura haemorrhagica occurring in an untreated case of syphilis.

Owing to the fact that Bismuth is frequently administered concurrently with the arsphenamine, it might be argued that the Bismuth was an aetiological factor in the development of post-arsphenamine purpura, but a perusal of the literature yields no record of such an incident.

In one of the six cases now reported the blood Wassermann was negative, the diagnosis of syphilis having been established by the presence of the spirochaeta pallida at the site of the primary lesion.
In this case no generalised infection could have taken place, and the vessel walls could not at this stage of the disease have been subjected to the toxic influence of the infection, yet in this case purpura haemorrhagica occurred.

It/

It seems therefore reasonable to conclude that the stage of the disease itself does not play a significant part in the aetiology of this type of purpura.

Increased permeability of the vessel wall probably does exist and may be a contributory factor in the haemorrhage, but it is unlikely that the syphilitic toxin is the cause of the increased permeability in the first instance.

(2) THE DRUG EMPLOYED, ITS DOSAGE, AND THE DURATION OF TREATMENT.

THE DRUG.

In all the six cases the particular brand of arsenic used was made by Burroughs Wellcome & Co. The Neoarsphenamine is known as "Neokharsivan", and the sulpharsphenamine as "Kharsulphan".

From Table V it will be observed that a combination of Neoarsphenamine and Sulpharsphenamine was used in four cases. In one case (No.2) Sulpharsphenamine was the only drug used, and in another (No.4) Neoarsphenamine was used alone.

Comparing/

TABLE V.

Case No.	Drug Employed.	Amount per dose and No. of Doses.		Total Arsenic		Average Weekly Dosage.
1	Neoarsphenamine	9.3 gm. (12)	0.15 gm. (1)	3.75 gm.)	7.65 gm.	0.28 gm.
	Sulpharsphenamine	0.3 gm. (12)	0.15 gm. (2)	3.9 gm.)		
2	Sulpharsphenamine only	0.3 gm. (25)	0.15 gm. (3)	7.95 gm.	7.95 gms.	0.29 gms.
3	Neoarsphenamine	0.3 gm. (1)	0.15 gm. (1)	0.45 gms.)	7.25 gms.	0.27 gms.
	Sulpharsphenamine	0.3 gm. (21)	0.15 gm. (3)	6.75 gms.)		
4	Neoarsphenamine only	0.45 gm. (11)	0.3 gm. (1)	5.25 gms.	5.25 gms.	0.43 gms.
5	Neoarsphenamine	0.15 gm. (8)	0.2 gm. (4) 0.3 gm. (4)	3.2 gms.)	6.87 gms.	0.2 gms.
	Sulpharsphenamine	0.3 gm. (8)	0.15 gm. (8) 0.075 gm. (1)	3.67 gms.)		
6	Neoarsphenamine	0.15 gm. (1)	0.3 gm. (5) 0.2 gm. (1)	1.85 gms.)	3.05 gms.	0.19 gms.
	Sulpharsphenamine	0.15 gm. (7)	0.075 gm. (2)	1.2 gms.)		

Comparing these two cases we find that 7.95 gms. Sulpharsphenamine was administered over a period of seven months, the average weekly dosage being 0.28 gm., whereas, 5.25 gm. Neoarsphenamine was given over a 3½ months. In the latter case the average weekly dose was roughly one gram greater than in the former. Assuming that the arsenic was responsible for the mishap, we might reasonably have expected the neoarsphenamine to cause the more severe reaction. Actually this was not so. Case No.2 died from extensive purpuric haemorrhages, whilst No.4 made a rapid and spontaneous recovery, after comparatively slight purpuric symptoms.

In Case No.3, 6.75 gms. sulpharsphenamine was given during a total series of twenty-four injections, whilst only 0.45 gms. neoarsphenamine was given during the same series of injections. When compared with the sulpharsphenamine, the amount of neoarsphenamine given in this case was so small that it might be entirely discounted. The average weekly dose of sulpharsphenamine might therefore be reckoned to be 0.2 gm.

Grouping Cases one, five and six together the total amounts of neoarsphenamine and sulpharsphenamine given amounted to 8.8 gms. and 8.7 gms. respectively. Therefore no definite conclusion can be reached from these cases as to which drug is the more toxic or which one the more likely to cause purpuric symptoms.

A/

A comparison of Cases 2 and 4 however suggests that sulpharsphenamine is the more dangerous drug. Case No.3 serves to show that comparatively small doses of this drug are capable of producing purpuric symptoms.

DOSAGE.

In no case did the dose of the drug administered exceed 0.45 gms. The average weekly dose was much below this. Compared with the usual doses given to patients in the early syphilitic stage, the average weekly dose in these cases was comparatively small.

The average total amount of arsenic administered was correspondingly small. In a first unit course of three months the patient usually receives about 4.2 gms arsenic.

In no case in the present series did any patient receive more than 3.9 gms. of arsenic during a unit course.

In three out of the six cases reported the onset of symptoms appeared during the third course of arsenical treatment.

In two cases, symptoms appeared during the second course and in one case symptoms did not appear until the fourth course of injections.

It would seem that neither the particular dose nor the total amount of arsenic administered can be regarded as solely responsible for the onset of purpuric symptoms.

It/

DURATION OF TREATMENT.

TABLE VI.

1	2	3	4	5	6
Case No.	Duration of Combined Arsenical and Bismuth Treatment.	Duration of Arsenical Treatment only.	Length of Rest Period from Arsenic prior to course in which purpuric symptoms occurred.	Total amount of Arsenic given in the course preceeding purpuric symptoms.	Interval between final injection of arsenic and the onset of pur. symptoms
1	21 months	8 months	7 months	1.35 gms.	2 hours
2	16 "	7 "	7 "	1.35 gms.	24 hours
3	18 "	8½ "	8 "	0.75 gms.	2 hours
4	4½ "	3½ "	1 month	1.35 gms.	2 days
5	27 "	8 "	12 months	0.375 gms.	12 hours
6	7 "	6 "	3 "	1.05 gms.	24 hours

It will be observed from Table VI (column V.) that purpura can occur after a comparatively small dose of arsenic. The patient (Case No.5) received no arsenic over a period of one year, yet the administration of three doses, amounting in all to 0.375 gms. Sulpharsphenamine was followed by purpuric symptoms.

The period of time over which the patients were treated with both arsenic and bismuth varied considerably. (Table VI).

The longest period was twenty-seven months (Case 5) and the shortest period 4½ months (Case 4).

The average duration of combined treatment was 15½ months.

Regarding treatment with arsenic alone, the average length of treatment was seven months.

The relationship between the duration of treatment and the mode of onset of symptoms is worthy of comment.

It will be seen from Table VI (column 6) that there is a tendency for symptoms to appear more suddenly in those cases longest under arsenical treatment.

The actual duration of the treatment however does not seem to be a factor in the causation of the complication.

Reference might be conveniently made at this point to/

to the relationship existing between the duration of treatment and the number of platelets.

An interesting comparison can be made, if these six cases are studied in two groups.

Group I comprises the cases treated over the longest period of time, (1, 3, 5).

Group II, those cases where treatment was of shorter duration, (2, 4, 6).

In Group I the average platelet count at the onset of symptoms was 352,000 per c.mm.

In Group II the average platelet count was 27,000 per c.mm.

It would therefore appear that the duration of treatment with arsenic has no effect upon the number of platelets in the circulation.

(3) TYPE OF INDIVIDUAL AND STATE OF HEALTH AT THE TIME OF ONSET OF PURPURA.

Five of the six cases now reported were females. The average age was thirty-eight.

With one exception the Blood Wassermann was positive, and the stage of generalised syphilis had been reached in all five cases. In no case was there any familial tendency to bleeding, and there was no haemorrhagic tendency in any of these patients.

There was no history of serious chronic ill-health

in any of the six patients, and they all appeared to enjoy normal health.

When the symptoms of purpura occurred, there was one outstanding pathological feature present in all the six patients. This was the presence of a septic focus of infection, the seat of the focus was in the mouth, or in the tonsils in five of these cases. In the one exception the seat of infection was in the ear.

Toxic Factors summarised.

Case I. The tonsils and gum margins were in a septic condition when purpuric symptoms occurred. The presence of non-haemolytic streptococci and staphylococcus (albus) was demonstrated in culture.

Case II. There was a history of frequent sore throat, the tonsils were enlarged and pus was present in both tonsils.

Case III. The patient suffered from sore throat for ten days prior to the onset of purpuric symptoms. The tonsils were enlarged and septic.
On culture haemolytic and non-haemolytic streptococci, staphylococcus albus and coliform bacilli were isolated from the tonsillar region.

Case IV./

Case IV. The right tonsil and the lower teeth were source of toxic infection, a culture from the lower gums showed the presence of non-haemolytic streptococci, and diphtheroid bacilli. A culture from the tonsil yielded a growth of non-haemolytic streptococci and staphylococcus albus.

Case V. The patient suffered from occasional sore throats before the commencement of anti-syphilitic treatment.
The teeth had been extracted three years previously because of pyorrhoea.
The tonsils were in a septic state and a culture showed the presence of non-haemolytic streptococci.

Case VI. The patient complained of a discharging ear, when she received her final injection of arsenic. The discharge had existed for fourteen days. There was no history of ear trouble prior to this time. On culture, a growth of staphylococcus albus, and coliform bacilli was obtained from the ear. The throat was congested and this yielded a profuse growth of streptococci viridans and staphylococcus albus.

It is obvious that in all these six cases, there existed, a state of chronic sepsis.

It is submitted that there exists a distinct relationship between these septic foci and the clinical picture of purpura haemorrhagica following the administration of arsenic.

Hitherto much importance has been attached to the presence or absence of thrombocytopenia. In nearly all the cases reported in literature of purpura haemorrhagica following arsenical treatment, the report is accompanied by the findings in the blood count, and the blood platelet count.

In these cases thrombocytopenia was almost invariably present, and stress has been laid upon this finding. But thrombocytopenia, per se, does not explain the occurrence of purpura - nor does it give us any conception of the pathogenesis underlying the condition.

MacKay (1931) found that in cases in which toxaemia existed, a reduction in the number of platelets frequently occurred. It may well be that the arsenic in the arsphenamines in the first instance, damages the capillary endothelium and a superimposed toxaemia causes a reduction in the circulating platelets, so that the damaged capillary walls then lack the protection of the platelets. If this is so, it would seem that the term thrombocytopenic purpura, as applied at present to

purpura/

purpura haemorrhagica following arsenical therapy, although of clinical and histological interest, has no pathological meaning. The essential feature is not the presence of thrombocytopenia, but the existence of some toxic factor which first causes thrombocytopenia. The all important factor would then be the degree of toxic infection. The more severe the toxaemia, the more marked will be the thrombocytopenia, and accordingly the more prolonged and severe will be the haemorrhage owing to lack of platelet protection to the vessel wall.

(4) THE ONSET OF SYMPTOMS.

Purpura haemorrhagica, in the course of arsenical treatment is a complication of sudden and dramatic onset. It usually occurs within a comparatively short time after an injection of arsenic. The onset however is seldom immediate, although such a case has been reported upon by S. Morton Smith. Generally, however there is a lapse of time, varying from a few hours to as many days, between the injection and the onset of symptoms. F.C. Combes (1927) reports on a case in which/

which this interval extended to twenty-one days, and E.T. Burke (1941) reports an interval of fifty-eight days in one of his cases.

In the series of six cases now reported two days was the longest interval to elapse, and two hours the shortest. The average intervals was 14⅛ hours.

In the cases taken from literature, omitting the two reported by Combes and Burke, these being quite exceptional in this respect, the average interval between the administration of drug and the onset of symptoms was four days.

It is impossible in the early stages to forecast with any degree of accuracy the prognosis of the case. Patients with comparatively mild early symptoms can rapidly become critically ill within a few hours of the onset of haemorrhage. There is very little clinical indication at the onset of the serious nature of the complication. Case No.2 in the present series serves to illustrate this point. The patient reported to hospital with purpuric haemorrhages on the buttocks and legs. Apart from this she was feeling well, with no other outward manifestation of her critical condition. The following day she became extremely ill, with extensive haemorrhage accompanied by shock. It happens not infrequently that the patient complains only of a few haemorrhagic spots or bruises and it appears impossible/

impossible to assess how much damage has been inflicted on the vascular and haemopoietic systems. It is thus essential to investigate thoroughly such prodromal symptoms as may occur. These may be slight and fleeting, but nevertheless they afford timely and certain warning of impending disaster.

The important and most frequent premonitory symptoms include:-

(1) Shivering (generally a few hours after an injection of arsenic).

(2) Malaise (within twenty-four hours).

(3) Sickness (immediate).

(4) Dizziness (immediate).

(5) Fainting (immediate).

(6) Vomiting (immediate).

(7) Skin rash, or patchy dermatitis.

(8) Headache (some hours).

(9) Vaso-dilator reactions (immediate).

Once established, the complication is characterised by haemorrhage, in one form or another. This usually takes the form of petechial haemorrhages into the skin, purpuric spots or ecchymosis. Bleeding frequently takes plaee from one or other of the mucous surfaces, it may occur in the viscera and from the serous surfaces. External haemorrhage most frequently takes place from the nose and from the gums.

Melaena and haematuria may occur if the complication/

complication assumes a severe degree. This occurred in Case No.2 of the present series, and it will be noted that this is the only case where there was complete absence of platelets.

The areas from which haemorrhage occurred in the six cases now reported are tabulated below.

TABLE VII.

Case No.	Skin.	Gums and Mucous Mem. of Nose and Throat.	Internal.
1	++	++	0
2	++	0	+++
3	+	0	0
4	+	++	0
5	++	0	0
6	+	0	0

0 = Nil. + = slight. ++ = moderate. +++ = Severe.

Haemorrhage into the skin was present in all the six cases. A moderate amount of haemorrhage from the gums and mucous membrane of the nose and throat occurred in two cases, and internal haemorrhage was severe in one case, which proved fatal.

(5)/

(5) ESSENTIAL FEATURES IN BLOOD EXAMINATION.

The blood findings in the six cases reported are given in Table VI.

Case 1. A moderate thrombocytopenia was present. Haemorrhage was not extensive or severe. There was no other abnormality found.

Case 2. The blood showed the presence of a very marked anaemia with great reduction of red cells. Leucopenia and granulocytopenia were marked features.
There was a complete absence of blood platelets. Haemorrhage was extensive and severe. The bleeding time was prolonged. The capillary resistance test was positive.
Although the patient was given five transfusions, she died nine days after the onset of symptoms.

Case 3. With the exception of a moderate degree of anaemia this patient presented a perfectly normal blood picture. Haemorrhage was not severe.

Case 4. A moderate degree of anaemia was present. The essential features were the presence of a leucocytosis and a severe thrombocytopenia. The bleeding time was definitely increased. Haemorrhage was moderately severe.

Case 5. Anaemia was present. The white cell count showed a leucocytosis, and the differential count a marked granulocytopenia. The platelet count was 556,000.

Haemorrhagic symptoms were not severe. The patient had not observed any frank haemorrhage. The patient did not report to hospital until seven days after the onset of his symptoms, and it is probable that after this interval of time the blood platelets would be restored to their normal numbers.

Case 6. Moderate Thrombocytopenia was the only feature present; although there was extensive haemorrhage into the skin, there was no bleeding from the mucous surfaces.

(See TABLE VIII)

TABLE VIII.

Case No.	Hb. %	Red Cells	White Cells	Poly-Morphs %	Lympho-cytes %	Eosino-phils.	Mono-cytes. %	Reticulo-cytes. %	Plate-lets.	Bleeding Time Mins.	Coagul. Time. Mins	Capillary Resistance.	Result.
1	68	3,520,000	5,800	78	20	1	1	1	200,000	4	5½	Positive	Recovered
2	27	1,590,000	3,600	30	65	3	2	2	Nil	15	7½	Positive	Died
3	60	4,500,000	8,740	72	25	1	2	.9	300,000	3	4	Neg.	Recovered
4	62	3,410,000	12,400	75	25	2	3	.9	25,000	12	4½	Positive	Recovered
5	56	3,010,000	13,500	28	66	2	5	1	556,000	4½	3½	Neg.	Recovered
6	65	3,000,000	4,200	68	30	1	1	0.5	56,000	5	3½	Neg.	Recovered

A study of the blood findings summarised in Table VIII indicate that:-

(1) Purpura haemorrhagics following arsenobenzol therapy can occur in the presence of a normal blood picture.

(2) In all cases of post-arsphenamine purpura there tends to be an anaemia of the secondary type. This anaemia is in no way distinctive.

(3) The severity of the haemorrhage appears to depend upon the degree of thrombocytopenia present.

(4) The bleeding time varies inversely as the number of circulating platelets.

(5) A negative capillary resistance test does not necessarily indicate the absence of purpura haemorrhagica. The test may be negative in the presence of purpuric symptoms.

(6) Periodic enumeration of the blood platelets during treatment with arsenic is of distinct value, as it may yield a clue to the patient's susceptibility to purpura.

(7) A study of the blood picture, made directly after the onset of purpuric symptoms is of great prognostic value.
Leucopenia, and an accompanying low polymorphonuclear count are unfavourable indications.

(8) The presence of a neutrophil leucocytosis may be regarded as a favourable prognostic sign.

(9)/

(9) If thrombocytopenia exists itself, without depression of the white cell elements of the blood the patient will probably make a spontaneous recovery. A persistent and severe thrombocytopenia is of serious import.

(6) SUGGESTIONS AS TO THE PREVENTION OF THE COMPLICATION.

(1) Before treatment is commenced a thorough search should be made for the presence of any toxic focus of infection. If such a focus be discovered no arsenical treatment should be administered until the source of infection has been completely eradicated. In all the six cases reported a toxic focus was present.

(2) A patient undergoing arsenical therapy should be thoroughly interrogated at each attendance as to any effect felt after any previous injection of arsenic. Prodromal symptoms were found in four of the six cases now reported.

Of the thirty-six cases reported upon from literature twenty-two of these experienced prodromal symptoms.

Should a history of some untoward reaction be elecited, the patient should not be given a further injection of arsenic, until such reaction can be satisfactorily proved not to have been due to arsenical intolerance.

(3) A complete blood examination should be performed before beginning treatment with arsphenamine. Where there is marked anaemia (below 60 per cent Haemoglobin), or an obvious diminution in the red or white cell count, treatment should be withheld.

(4) Every patient undergoing arsenical treatment should have a blood examination done periodically. The presence of thrombocytopenia indicates that a destruction of platelets is taking place.
If thrombocytopenia is present, a daily estimation of the platelets should be made.
A mild leucocytosis may indicate the presence of a toxic factor.

(5) A patient showing a marked thrombocytopenia (below 200,000, or a decrease in the number of polymorphonuclear cells should be hospitalised.

(6) The substitution of mapharsan (obtained by the oxidation of arsphenamine) in place of the arsphenamines appears worthy of trial. Falconer and Epstein (1936) report favourably upon the former drug. Five cases who exhibited symptoms of purpura after the arsphenamines, were tested for sensitivity to mapharsan. In no instance was there any constitutional reaction, or any untoward reaction after mapharsan.

(7)/

(7) Since the introduction of arsphenamine in the treatment of syphilis various workers have attempted to reduce the toxicity of the drug, and thus lower the incidence of such reactions as post-arsphenamine purpura.

The method adopted has been to add to the solution of the arsenic, or to administer concurrently, some substance which would be thought an improvement on the arsenic itself.

The substance perhaps most frequently used in this way has been glucose, and many workers have claimed that it reduces the toxicity of the arsphenamine. Calcium in the form of calcium gluconate, and sodium thiosulphate have also been widely recommended for use with arsenic.

Doak (1941), who has made an extensive survey of the literature apppertaining to this particular aspect of arsphenamine therapy comes to the conclusion that, so far the clinical results are inconclusive, and that in spite of the many combinations that have been suggested none have been conclusively shown to have any advantage over arsphenamine solutions alone.

(7) TREATMENT OF THE ESTABLISHED CONDITION.

Any discussion of the treatment of post-arsphenamine purpura must take into consideration the fact that a large number of cases recover spontaneously. Five of the six cases now reported fall into this group.

In the absence of any certain understanding of the aetiology of this form of complication, treatment must be more or less empirical. It is therefore expedient to adopt any line of treatment that might reasonably be expected to afford relief of symptoms.

As a result of haemorrhage, the patient may lose, in a comparatively short time, a considerable amount of blood. In this form of purpura the initial bleeding may be slight but it is impossible to judge clinically to what extent further haemorrhage may take place within a very few hours.

Depending upon the extent of haemorrhage the patient may suffer from shock, this, along with our uncertain knowledge as to how serious the reaction may become, is sufficient justification for the immediate hospitalisation of the patient.

It is essential that a blood count should be done in order to assess:

(1) the extent of anaemia present.

(2) the degree of thrombocytopenia, if any

and (3) the extent to which the bone marrow is affected, if at all.

The most serious symptom is the presence of haemorrhage. The extent of bleeding may vary from a few petechial spots to very extensive haemorrhage from the mucous membranes, and viscera. An alarming feature of post-arsphenamine purpura haemorrhagica is the uncertain nature of its pathology, and the unknown extent to which haemorrhage may take place. Therefore in every case, no matter how slight, the first essential is to endeavour to avert such haemorrhage as may exist, and to combat anaemia. A variety of therapeutic agents have been used, all with this object in view, and opinions differ widely as to their value.

Transfusion in post-arsphenamine purpura.

Case No.2 of the present series was transfused five times with one pint of blood. The patient received her first transfusion the day after she was admitted to hospital, and as soon as it was seen that the haemorrhage was likely to be extensive. In this case the blood picture denoted severe damage to the haematopoietic system, and this was present when the patient came into hospital, i.e. three days after the onset of symptoms. Had this patient reported to hospital at the onset of her first symptoms transfusion might have saved her.

In one case reported by Moore and Keidel (1921) the patient/

patient was first transfused eleven days after the onset of symptoms. This patient was transfused with 250 cc. citrated blood on four occasions. As a result of this there was a marked increase in the haemoglobin and red cells, but nevertheless the patient died four weeks from the onset of symptoms.

Dodd and Wilkinson (1928) reviewed twenty-four cases of severe granulocytic aplasia of the bone marrow after arsphenamine treatment. Twenty of these showed signs of purpura. Transfusion Therapy was tried in six cases of purpura, but in no case was there any improvement.

Peck, Rosenthal and Erf (1936) report on two cases of acute purpura haemorrhagica. In spite of many blood transfusions, both patients died.

Jones and Trocantins (1936) report on twenty-two cases of purpura haemorrhagica, all of which were treated with blood transfusion. In eight cases the treatment was entirely successful. In seven cases the result was only temporarily beneficial, and in seven cases the transfusion failed to have any effect on the course of the disease. These authors conclude that "contrary to their former opinion" transfusion treatment is not always effective even when given under the best conditions.

The present position may be summarised by saying that although blood transfusion has been found to benefit the anaemic condition of the patient in cases of/

of purpura, the bulk of evidence appears to show that no constant or beneficial effect can be confidently anticipated as a result of blood transfusion in cases of post-arsphenamine purpura.

Platelet Response to X-Ray Therapy. Mettier and Stone (1936) report on six cases of thrombocytopenic purpura treated with X-Ray to the spleen and one with X-Ray over the long bones. The dose was 200 to 300 units given daily for six to fifteen days. These authors state that prior to treatment the platelet count varied from 10,000 percmm. to 40,000 per c.mm. Six of these patients showed an increase in platelets beginning within twenty-four to forty-eight hours, the platelet count reaching between 250,000 per c.mm. and 500,000 per c.mm. in nine days.

Davidson (1936-1937) submitted three cases suffering from thrombocytopenic purpura to X-Ray treatment, the dosage being that suggested by Mettier and Stone (1936). No significant change however was noted in the platelet count in any of the three cases.

Further investigation of this form of treatment is necessary before any conclusion can be reached regarding its efficacy.

Liver. Jacob and Clapperton (1930) claim to have cured one patient suffering from throbocytopenic purpura with liver extract after failure to obtain/

obtain satisfactory results with collosal calcium and haemoplastin.

Box and Massingham (1931) report upon the effect of liver therapy used in one case of purpura haemorrhagica complicating Scarlet Fever. These authors claim that liver causes a rapid and progressive increase in the number of blood platelets, and in the case treated there was an obvious improvement in the haemorrhagic symptoms within twelve hours.

Witts, J.L. (1931) reports in five cases of thrombocytopenic purpura treated with liver. None of these cases derived any benefit from the treatment. In no case was there any permanent increase in the number of platelets, and all the patients continued to bleed during the liver treatment.

In my own series of cases, liver therapy was used in one patient. The liver was given at the same time as the blood transfusion. The patient received 5 cc. Pernaemon Forte on four occasions over a six day period. The patient continued to bleed freely, there was no improvement in her symptoms, she finally became comatose and died five days after the institution of liver therapy.

Such evidence as at present exists appears to support the view that liver therapy has no power to diminish the haemorrhage, or to increase the platelets in thrombocytopenic purpura.

Parathyroid Gland. Lowenburg and Ginsburg (1932) report the result of their observations after parathyroid extract had been administered in two cases of thrombocytopenic purpura.

In one case it was noted that on the second day of parathyroid administration, the bleeding time fell from over two hours (noted on admission) to between five and six minutes, and all visible haemorrhage had ceased.

In the second case, (after over a month's treatment with moccasin snake venom, without clinical improvement) parathyroid extract was administered. Following this treatment clinical improvement was noted and the bleeding time was markedly decreased.

These authors claim that after hypercalcaemia was established there was a rise in the blood platelets and clinical cure followed in both cases.

Mathewson and Cameron (1937) treated one case of idiopathic purpura haemorrhagica with intramuscular injection of parathormone (Lilly). This treatment produced practically no effect on the blood serum calcium, nor was there any rise in the blood platelets.

This form of treatment has not had sufficient clinical trial to permit any definite conclusions being formed.

Snake Venom. Peck and Rosenthal (1935) suggest that the venom of the Moccasin snake, used in solution of 1 in 3000 in physiological saline/

saline is of value in the treatment of purpura haemorrhagica. The initial injection in patients over ten years is 0.4 c.cm. subcutaneously, increased to 1 cc. as a maximum dose. This is usually given twice weekly, and if symptoms are severe every third day.

Nine cases of purpura haemorrhagica with typical and marked symptoms were treated with snake venom.

The majority of patients showed a definite response to the treatment. Three other cases of purpura haemorrhagica were similarly treated, but in these the venom was ineffective in checking the haemorrhage.

These authors conclude that snake venom diminishes the bleeding in certain cases of purpura haemorrhagica, but it in no way affects the blood picture.

Greenwald (1935) has used this venom in three cases suffering from purpura,with satisfactory results. The results showed that actual bleeding stopped in all three patients after the third or fourth injection. The cardinal signs of thrombocytopenic purpura were present in each case at the first examination. After the injections of snake venom the bleeding time became normal in all the three cases.

In two patients the capillary resistance test which was strongly positive at the first examination, became negative after two months.

Peck, Rosenthal and Erf (1936) studied the effect of subcutaneous injections of Moccasin snake venom in

thirty-two/

thirty-two cases of chronic purpura haemorrhagica. These authors claim symptomatic improvement in seventeen of their cases, four cases failed to show any response, and eleven cases required either splenectomy or ligation of the splenic artery.

Davidson (1936-1937) endeavoured to obtain successful results in three cases of thrombocytopenic purpura with bi-weekly injections of snake venom given according to the instructions published by Rosenthal. In no case was there any improvement noted.

Lowenburg and Ginsburg (1936) failed to obtain any success in a case of thrombocytopenic purpura treated with mocassin snake venom for over a month

A final conclusion cannot at present be reached regarding the efficiency of snake venom as a therapeutic agent in post-arsphenamine purpura. There seems to be a considerable diversity of opinion among competent observers as to the efficacy of this form of treatment and critical evaluation of the results is difficult.

Calcium. In case No.5 of the present series, the patient received fifteen bi-weekly injections of 1 cc. Colloidal Calcium. Seven days after the final injection of calcium, arsenical treatment was started. The patient had received only three small doses of sulpharsphenamine before purpuric symptoms developed.

The/

The inference is that calcium is not effective in preventing the onset of purpuric symptoms.
Gorrie (1940) reports no success with calcium gluconate given intramuscularly.

Vitamin C. Miller and Rhoades (1936) have studied the therapeutic effects of Vitamin C in a group of patients suffering from thrombocytopenic purpura. In four cases a persistent rise in the number of thrombocytes and complete relief from symptoms followed the administration of ascorbic acid. In two instances the clinical improvement was associated with an increased urinary output of ascorbic acid.
Davidson (1936-1937) on the other hand failed to obtain a satisfactory result in any of these cases of thrombocytopenic purpura which he treated with ascorbic acid.
Witts (1937) reports no success in three cases of thrombocytopenic purpura after treatment with vitamin C.
Vaughan (1937) treated one case of thrombocytopenic purpura with ascorbic acid, but failed to produce any beneficial effect.
Wright and Lilienfeld (1936) studied the effect of the administration of crystalline vitamin C, in two cases of thrombocytopenic purpura haemorrhagica: although large doses of cevitannic acid was given, there was no evidence of a favourable effect in the clinical/

clinical course of the illness.

Scarborough (1942) states that he has recently treated seven cases of thrombocytopenic purpura with massive doses of ascorbic acid, without any demonstable effect on either the blood platelets, the bleeding time or the capillary resistance.

Vitamin C has therefore had an extensive trial in the treatment of thrombocytopenic purpura. The majority of observers have failed to find any clinical benefit resulting from its use in this form of purpura, and it does not appear probable that the administration of Vitamin C would be of value in the treatment of post-arsphenamine purpura.

Vitamin P. Scarborough and Stewart (1938) investigated the therapeutic effect of Vitamin P in six cases, all suffering from a deficiency of one or more vitamins in the diet. In three of these cases, spontaneous haemorrhages were present when they first came under observation and all three were being treated with arsenic or bismuth for syphilis.

Hesperidin (Vitamin P. Glaxo) was administered orally in doses of 1 gramme per day.

As a result of their investigations, these authors believe that Vitamin P can reduce the number of haemorrhages in patients who suffer from a vitamin deficiency.

Gorrie/

Gorrie (1940) reports favourably upon the use of Vitamin P in his case of purpura haemorrhagica after arsenical treatment. This vitamin was administered by the mouth in doses of 0.25 gms. at two hourly intervals. After a total of 5.75 gms. no further bleeding was noted.

Scarborough (1942) believes that a deficiency of Vitamin P may produce a clinical syndrome in some way analogous to purpura haemorrhagica, the salient features being petechial bleeding, a slightly prolonged bleeding time, and a low capillary resistance.

Before the administration of Vitamin P can have a rational basis in the treatment of purpura haemorrhagica following arsenical therapy, it would first of all have to be established that increased capillary fragility is a constant and important factor in the aetiology of the condition.

If a decrease in the number of blood platelets leads to an increase in the bleeding time and also to haemorrhage, it follows that treatment should be directed towards increasing the number of platelets.

Schiff and Hirschberger (1937) claimed to have increased the number of platelets in normal and thrombocytopenic children by the administration of a fat soluble factor which they have designated for the time being, the "T" factor. This factor was found to be active in sesame/

sesame oil eight to ten drops of which produced a notable rise in the platelet count.

I have been unable to find any further reference to or confirmation of this work.

It would appear that the various forms of treatment enumerated have been effective at one time or another in cases of thrombocytopenic purpura, and it would seem reasonable to apply such treatment in cases of post-arsphenamine purpura. But it must be admitted that until now, no method or substance has been found uniformly beneficial in these cases.

SECTION IV.

CONCLUSIONS.

(1) Post-arsphenamine purpura is an acute complication which may occur in any patient undergoing anti-syphilitic treatment. It may occur at any stage in the disease. It is however more likely to develop after a series of arsenical injections have been given, rather than in the early stages of treatment.

(2) A complete study of the blood picture is necessary before the nature of the complication can be identified.

(3) From a general survey of literature, and a particular study of the six cases in the present series, there seems a probability that the arsphenamines are capable of exerting damage on the capillary endothelium, but this does not appear to be the only factor of aetiological importance in post-arsphenamine purpura.

(4) Neither the amount of the drug, the individual dose, or the duration of arsenical treatment are factors of aetiological importance.

(5) A study of the six cases reported suggests that the longer the duration of treatment with arsenic, the more sudden is the onset of the purpuric symptoms.

(6) The onset of post-arsphenamine purpura cannot be anticipated clinically. In the majority of cases it occurs within thirty hours after the arsenical injection, although in exceptional cases it may be delayed.

(7) The early clinical signs in post-arsphenamine purpura give no indication as to the future course of the reaction.

(8) One sex is no more prone to the complication than the other. The majority of cases occur between the third and fourth decades of life. A probable explanation of this is that syphilis is relatively more common between the ages of thirty and forty, and the majority of patients undergo treatment during this period.

(9) In all the six cases now reported, a focus of toxic infection was found present, and a state of chronic infection existed in these patients.

(10) Thrombocytopenia is not always present in post-arsphenamine purpura, and purpuric haemorrhages may take place in its absence. Thrombocytopenia is not the responsible factor in post arsphenamine purpura, although the extent of haemorrhage may be determined by the degree of thrombocytopenia present.

(11)/

(11) It is suggested that the state of toxaemia which existed in these cases was primarily responsible for the occurrence of the complication, and that the thrombocytopenia was the result of a toxaemic condition.

(12) Before arsphenamine treatment is instituted for syphilis, a thorough search should be made for the presence of any toxic focus of infection. No arsenical treatment should be administered before such a focus, if found, is completely eradicated.

(13) Prodromal symptoms are present in the majority of cases of post-arsphenamine purpura. Should a history of such symptoms be obtained, it is an indication that the administration of arsenic should cease.

(14) Comparatively small doses of the arsphenamines can produce purpuric symptoms, even after a prolonged period of rest from the drug. A patient having once shown signs of post-arsphenamine purpura should not be subjected to further treatment with arsenic, until it is reasonably certain that no source of toxaemic infection exists.

(15)/

(15) Any patient who exhibits even the milder manifestations of purpura haemorrhagica after arsenical treatment should be immediately hospitalised, and a complete examination of the blood should be made as early as possible.

(16) Specific or standardised treatment of post-arsphenamine purpura has not yet been established. Blood Transfusion improves the anaemic condition of the patient, but does not arrest the haemorrhage, or in any way help to repair a damaged haematopoietic system.

X-Ray Therapy. Liver Extract. Parathyroid Extract: Each of these agents have been used in cases of thrombocytopenic purpura. The reports on the clinical results obtained are conflicting and no precise conclusion can be reached regarding their therapeutic value in post-arsphenamine purpura.

Calcium. The administration of calcium salts, either before or after the onset of purpuric symptoms has not given satisfactory results.

Snake venon administered subcutaneously appears to be of therapeutic value in checking the haemorrhage in some cases of purpura haemorrhagica, but the results obtained with this agent have not been uniformly successful.

Vitamins./

Vitamins C. and P. The value of vitamin C. in purpura haemorrhagica is at present open to doubt. There is scant evidence on which to justify its use in post-arsphenamine purpura.

The administration of vitamin P appears to reduce the number of petechial haemorrhages in cases of post-arsphenamine purpura where an increased capillary fragility is associated with a vitamin P deficiency.

(17) It is suggested that the incidence of post-arsphenamine purpura could be greatly reduced, if efficient prophylactic measures were adopted. This involves:

(1) a thorough and systematic search for the presence of a toxic focus of infection in every patient undergoing arsphenamine treatment for syphilis.

(2) a careful inquiry as to the occurrence of any untoward reaction following the injection of an arsenical preparation.

(3) a complete examination of the blood, this being performed at frequent intervals during each course of arsenical treatment.

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