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ESSENTIAL PURPURA HAEMORRHAGICA *

BY

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Cases of purpura have been reported from the earliest times, and a recent writer has even quoted instances in the Bible. No doubt scurvy and purpura have sometimes been mixed up, but it is evident that definite cases of purpura haemorrhagica occurred thousands of years ago.

In modern times the first to describe the clinical symptoms of purpura was Paul Werlhof (1699-1767), a German physician, who wrote of it in 1735 as "morbus maculosus," as stated by Professor I. Abt.¹ Johan L. Schönlein, born in 1793, described peliosis rheumatica, while another distinguished physician, Edward H. Hensch (1820-1910), described purpuric symptoms accompanied by pain in the abdomen, vomiting, fever, and the passage of blood in the stools. He was aware that in some instances it was associated with rheumatic pain and swelling. The names of Donne, Schultze, Sir William Osler, and Bizzozero are noted in the literature; and Georges Hayem described the platelets, which he stated were much concerned with clotting of the blood. It was in 1889 that Denys recorded that the blood platelets were diminished in purpura haemorrhagica. W. W. Duke of Johns Hopkins University was the first to describe the prolongation of the bleeding time in the disease. E. Glanzmann (University of Berne) was of opinion that the Schönlein and Hensch types of purpura were anaphylactoid. E. Frank (University of Breslau) described the disease as essential thrombopenia. He was of opinion that purpura could not occur without some damage to, or increased porosity of, the capillaries. Finally, great credit is due to Paul Kaznelson, who in 1916 was the first to suggest splenectomy for purpura haemorrhagica, and certainly there have been some brilliant results from this operation when performed in suitable cases.

* Delivered at the Biennial Conference of the New Zealand Branch, British Medical Association, February, 1935.

¹ *Amer. Journ. Dis. Child.*, February, 1935.

Varieties of Purpura.—Purpura is usually divided into (a) primary, and (b) secondary. Examples of the secondary type are certain blood diseases such as leukaemia, pernicious anaemia, and aplastic anaemia; haemolytic jaundice, Gaucher's disease, carcinomatosis of the bone marrow; infections such as cerebro-spinal fever; and the type following the use of chemical substances such as iodine, benzol, etc. The primary form can be subdivided into (1) haemorrhagic purpura (purpura simplex, purpura haemorrhagica, and purpura fulminans), and (2) anaphylactoid purpura (Henoch's and Schönlein's purpura). It seems certain that some of the cases of anaphylactoid purpura, and also a number of cases designated as haemorrhagic purpura, are by no means all primary, and future investigation will demonstrate which cases are really primary.

Essential Purpura Haemorrhagica

In this type, in addition to the purpuric spots present in the skin and mucous membrane, there is also bleeding from one or more areas of mucous membranes, such as the nose, gums, mouth, uterus, urinary tract, intestinal tract, stomach, etc. The haemorrhages may be accompanied by anaemia, which is sometimes severe. Occasionally a raised temperature is present. The general condition of the patient may be stated to vary in accordance with the loss of blood.

In my experience *the spleen is not enlarged* in these cases either clinically or as seen at operation or after examination by the pathologist. Of course there may be cases in which the spleen is enlarged temporarily. Certain tests are invaluable in the elucidation of this type—thus the presence of *thrombocytopenia* (the platelets being reduced from the normal figure of about two to three hundred thousand to forty thousand or less, and sometimes no platelets being seen at all for a time; *increased bleeding time* (from what is usually accepted as normal—namely, three to four minutes) up to twenty to thirty minutes or even ninety minutes or more in rare cases; a *positive capillary resistance test* (estimated by placing a rubber bandage or the armlet of a blood pressure instrument around the upper arm and keeping the pressure midway between the systolic and diastolic for three minutes, when, if positive, haemorrhagic areas appear between the wrist and the lower end of the bandage). There is also described a *flat-topped blood clot*, but this cannot be looked upon as diagnostic, for it is present in a number of other complaints. The blood coagulation is practically normal, in marked contrast with haemophilia.

Acute, chronic, and intermittent forms of essential purpura haemorrhagica are described. The disease should always be looked upon as a serious malady, for a case which may not appear to endanger the life of the individual may terminate with tragic suddenness.

Two Case Reports

I have had five typical cases of essential purpura haemorrhagica, all of which have been cured by splenectomy. The notes of two, both of which were operated on nine and a half years ago, are recorded below.

CASE I

Winnie B., aged 10 years, was admitted to the Royal Waterloo Hospital on 12/7/25. She was bleeding from the gums and nose, and a number of purpuric spots were present on the body and also some bruises. During the previous year she had attended the hospital for purpura as an out-patient.

Examination.—The patient was suffering from continuous oozing from the gums, which did not respond to any treatment. The temperature was 98.6° F., pulse 106, and respirations 24. Nothing abnormal was observed in the heart, lungs, or abdomen. The tonsils were enlarged. She was subject to

constipation. There was no history of melaena, and no known case of purpura existed in the family.

Further Observation.—12/9/25: Transfusion of 150 c.cm. of 0.25 per cent. citrated blood. 27/10/25: Much improved since transfusion, but gums still bleeding. Haemoplastic serum 2 c.cm. given intravenously, also calcium salts by the mouth. Both were quite useless. 30/10/25: Joint pains present. Spleen not palpable. 31/10/25: Red blood corpuscles, 3,900,000; haemoglobin, 45 per cent.; colour index, 0.5; white blood corpuscles, 5,000 (polymorphs 44 per cent., lymphocytes 53 per cent., eosinophils, 1 per cent., transitional cells 2 per cent.); no platelets seen; the red corpuscles were reported as very pale; anisocytosis was present. 10/11/25: Red blood corpuscles, 4,984,000; haemoglobin, 42 per cent.; colour index, 0.43; no normoblasts or megalo-blasts; average size of corpuscles not increased. White blood corpuscles, 4,800 (mast cells 2 per cent., leucoblasts 3 per cent., and lymphoblastic plasma cells 2 per cent.); only two blood platelets were seen in each whole slide. Bleeding time was twenty minutes; capillary resistance test positive. Nothing abnormal was found in the urine or faeces, and there was no evidence of any primary cause.

Diagnosis and Treatment.—With such a clinical history, and with thrombocytopenia, prolonged bleeding time, and a positive capillary resistance test, the diagnosis of essential purpura haemorrhagica could be made. As the gums had been bleeding for over eight weeks and no treatment had had any effect in stopping it, I asked Mr. Maingot to perform splenectomy, which he did on 13/11/25. The following are the blood picture figures immediately following the operation.

Date	R.B.C.s	W.B.C.s	Hb %	Platelets	C.I.
14/11/25	4,800,000	26,000	30	50,000	0.3
16/11/25	5,620,000	21,600	65	281,000	0.6
21/11/25	5,584,000	11,200	68	310,000	0.6

Five per cent. of the myelocyte group were present on November 14th, but none were seen on 19/11/25. Four of us noted that within ten minutes of the clamping of the splenic vessels oozing from the gums ceased. It has never recurred. The patient made an uninterrupted and perfect recovery.

Spleen Examination.—Dr. K. Gordon observed endothelial proliferation in the spleen and the presence of phagocytic cells. Since the operation the capillary resistance test has been carefully done every six months, and has always been negative. The bleeding time has been between three and four minutes; the clotting time was about four and a half minutes. Further progress is shown in the table below (a blood count made by Dr. Knott).

	10/2/30	24/2/31	21/11/32	10/9/34
Red cells ...	4,100,000	4,460,000	4,650,000	4,500,000
Haemoglobin ...	72%	82%	79%	82%
Colour index ...	0.88	0.98	0.84	0.91
White cells ...	6,200	6,750	6,700	7,000
Polymorphs ...	36%	50%	51%	66%
Lymphocytes ...	41%	36%	36%	24%
Hyalines ...	20%	10%	10%	7%
Eosinophils ...	3%	3.5%	2%	2%
Basophils ...	—	0.5%	1%	1%
Platelets ...	120,000	175,000	110,000	128,000

Result.—A letter received from the patient early last October stated that she had enjoyed the best of health and had been quite free from purpuric spots since the operation, there had been no signs of bleeding from mouth or nose, and that menstruation was regular and normal. No excessive bleeding had followed dental extraction. Recent examination of this patient confirmed the excellence of her health. She is able to work at a milliner's from 9 till 5 daily without any ill effects or any symptoms of exhaustion.

CASE II

Mrs. E. D. was first admitted to the Royal Waterloo Hospital in 1909, when 13 years old. The notes state that she had a "black-red" rash all over her body, and that two days before admission there had been considerable bleeding from the throat and nose and an effusion of blood under the right sclerotic; slight abdominal pain had been complained of, and the vomited blood had always been clotted.

Early History.—Four years previously, when 9 years of age, severe epistaxis occurred without any other symptom. I suggest that this was her first symptom of purpura. No other member of her family suffered from purpura. On examination a haemorrhagic rash was found scattered all over the body and limbs, but not on the neck. She suffered from an attack of severe epistaxis, the bleeding being eventually controlled by plugging. Loss of blood made her distinctly anaemic. The urine was dark red, and contained much blood. The case notes on 29/6/09 state: "Blood-stained discharge from left ear; gums swollen and bleeding, fresh crop of purpuric spots." On 5/11/09 the report is: "Conjunctival haemorrhage in left eye. No albumin in the urine; child still bruises easily." During the period she was in hospital the temperature was usually normal, only occasionally going up to 99° F. The pulse varied from 80 to 130. Menstruation began at 13, lasting usually five days, and occurred every three to five weeks. Floodings, lasting from two to three days, sometimes accompanied the menstrual flow from the age of 14 to 16. The periods were normal from 16 until she was 24. She was married at 23, and had a baby during the next year. After the birth there were haemorrhages from the gums and purpuric spots on the trunk, limbs, face, and right eye. Several ecchymoses were present. There was a markedly blood-stained discharge from the vagina. The heart was normal in size and rhythm. Other notes on the case state that on 5/10/21 the catheter specimen of urine contained a good deal of blood, there being marked bleeding from the uterus and vagina. At this time there were fresh petechiae on the body, and the gums were again oozing. On 18/10/21 the patient passed a large blood clot the size of a hen's egg; her colour was described as worse, and she felt weaker. Temperature and pulse were raised. Examined under an anaesthetic at this time an offensive blood clot was removed from the vagina and a swab from the uterine cavity contained a few streptococci and some *B. coli*. Pituitrin was given, also normal horse serum, and then transfusion of human blood and antistreptococcal serum. Later haemostatic serum was tried, followed by a sensitized *Streptococcus pyogenes* vaccine. The only thing that had any effect in stopping the bleeding was the blood transfusion. The subsequent history shows that the patient suffered on and off from attacks of purpura, sometimes markedly severe, and menstruation was so dreaded on account of severe loss of blood that she always sought admission to hospital during her periods.

Author's Examination.—I first saw the patient in September, 1924. She was a typical case of purpura haemorrhagica. The bleeding time was seventeen minutes, and the capillary resistance test markedly positive after two and a half minutes. Platelets were almost completely absent, blood coagulation time being two minutes twenty seconds. The blood count varied directly with the bleeding, being sometimes normal, but after a very severe haemorrhage it showed a red cell count of just over two millions. There was nothing special about the differential count except that sometimes the lymphocytes were a little raised and the polymorphs a little down. No abnormal red cells were seen. Platelets varied from one or two hundred thousand to nil.

Further Observation and Treatment.—During the next fifteen months I carefully observed her condition, and found that the only treatment which effectually stopped the bleeding for the time was the transfusion of 0.25 per cent. citrated blood. The good effect of this, however, only lasted from ten to fourteen days, when there was a gradual recurrence of symptoms. The case being one of essential thrombocytopenic purpura haemorrhagica and her life being in danger, I therefore asked Mr. Maingot to do a splenectomy. This was performed on 15/1/26. At no time had the spleen been palpable, and at operation it was found to be of normal size. Blood from the splenic artery and vein was obtained at the

operation for platelet count by Dr. Knyvett Gordon, the figures being 325,000 and 65,000 respectively. Two days after the operation the platelets rose to 197,000, and a few days later to 300,000 per c.mm.

Result.—On 2/2/26 the capillary resistance test was quite negative. No purpuric spots and no haemorrhages from mucous membrane have occurred since operation. The patient has been in perfect health since the operation nine and a half years ago, and quite free from any symptom of purpura. The menstrual periods have been normal in every way. The bleeding time has been normal, and the capillary resistance test constantly negative. Since splenectomy she has had several teeth extracted with only the usual loss of blood, and even a miscarriage a few years ago was accompanied only by normal loss of blood, thus contrasting markedly with the severe loss of blood after the birth of her child previous to splenectomy. On 5/9/34 Dr. Knott did a blood count, which showed: red cells, 4,540,000; haemoglobin, 76 per cent.; colour index, 0.83. The white cells were 6,600 (polymorphs 60.5 per cent., eosinophils 2 per cent., basophils 0.5 per cent., and lymphocytes 31 per cent.). The platelets numbered 185,000. The red cells were reported to be a little pale. A letter from the patient a few months ago stated that since the operation she had gained weight and felt in excellent health.

Collected Data in Five Cases

It may be of interest here to record a few observations based on my five cases of essential purpura haemorrhagica. Of the five patients four were female and one male. The ages at which the first symptoms were noted were: Case 1, 9 years; Case 2, 9 years; Case 3, 6 years; Case 4, 6 years; Case 5, 9 years. The age when splenectomy was performed was: Case 1, 10 years; Case 2, 28 years; Case 3, 6 years; Case 4, 6 years; Case 5, 11 years. The duration of symptoms at time of operation was: Case 1, one to four months; Case 2, over seventeen years; Case 3, one month; Case 4, four days; Case 5, one to four months. Cases 3 and 4 were acute, and the remaining three chronic. The time that has elapsed since splenectomy is as follows: Case 1, nine and a half years; Case 2, nine and a half years; Case 3, nine and a half years; Case 4, four years; Case 5, two years. There has been no return of purpuric symptoms in any of the five cases since splenectomy. Ordinary knocks have caused no bruising since splenectomy, contrasting with severe and easy bruising previously. The present health of all five patients is perfect. Case 2, which suffered from severe menorrhagia previous to splenectomy, has had normal menstruation since. Case 1 has commenced menstruation since splenectomy, which is always normal and never excessive.

Below platelet count, bleeding time, and capillary resistance are set out in tabular form.

Platelets

Case Number	1	2	3	4	5
Lowest count before operation	0	? 0	0	16,000	20,000
Count five days after operation	166,000	300,000	250,000	90,000	150,000
Count from splenic artery and vein at operation	?	A.—325,000 V.—65,000	A.—163,000 V.—56,000	?	?

Bleeding Time

Case Number	1	2	3	4	5
Before operation (time in minutes)	23	17	15	90	20
Time after operation	Normal	Normal	Normal	Normal	Normal

Capillary Resistance Test

Case Number	1	2	3	4	5
Before operation ...	Positive	Positive	Positive	Positive	Positive
After operation ...	Negative	Negative	Negative	Negative	Negative

Statistics

John de J. Pemberton, in *Collected Papers of the Mayo Clinic and Foundation*, stated that from 7/3/23 to 1/1/31 splenectomy was performed for purpura haemorrhagica at the Mayo Clinic in forty-one cases, with two deaths. Of the thirty-nine living patients thirty-six were reported well, two fair, and the condition of one poor. I am indebted to the Librarian of the Royal College of Surgeons of England for the following information sent to me during September, 1934. The total cases of thrombocytopenic purpura haemorrhagica for which splenectomy had been performed which he traced was 233. Of these there had been 173 cures, thirty deaths, one incomplete cure, seventeen improved, six unimproved, and six unknown.

Diagnosis

One might describe essential purpura haemorrhagica as an idiopathic disease, which may be acute or chronic and intermittent. It is characterized by the appearance of purpuric spots on the skin and spontaneous haemorrhages from one or more mucous surfaces—often resulting in anaemia—in which there are prolonged bleeding time, distinct diminution in the number of platelets, a positive capillary resistance test, generally a normal coagulation time, and a flat blood clot. The differential diagnosis has to be made from haemophilia, aplastic anaemia, lymphatic leukaemia, scurvy, hereditary haemorrhagic telangiectasis, and also from symptomatic purpura and hereditary thrombasthenic purpura. The points of importance are the personal and family history, the clinical history of the case, the performance of careful clinical examination, complete blood investigation, and the various tests mentioned above, such as bleeding time, coagulation time, etc. A proper appreciation of the information afforded should determine the diagnosis.

Prognosis

Before splenectomy was performed for this complaint there was always a distinct risk of a grave ending, which may occur quite suddenly. In my experience both acute and chronic cases are suitable for operation provided the diagnosis is definitely established. It is a matter of some importance that search should be made at the operation for accessory spleens, and that, if found, they should be removed lest their presence determine a recurrence of purpura. In my own experience all five patients remain in perfect health and quite free from any symptoms since splenectomy, which in three instances was done over nine and a half years ago.

Treatment

As a temporary measure in severe bleeding from purpura haemorrhagica blood transfusion is distinctly valuable in stopping the haemorrhage, but the good effects are only likely to last for from ten to fourteen days. In my own experience neither drugs nor thromboplastic serum are of any real use. Tying the splenic vein has been practised by some, but if the causative agent should prove to be a toxic substance present in the spleen splenectomy is preferable. Splenectomy in suitable cases is the treatment to be adopted. At the same time the operation should never be lightly undertaken, as is sometimes sug-

gested, without due regard to all circumstances of the case, in the same way that obtains before appendicectomy or tonsillectomy is performed. I know of an unusual case of leukaemia, diagnosed incorrectly as essential purpura haemorrhagica, in which splenectomy was performed with quickly fatal results. It is wise to put normal saline solution into the peritoneal cavity before closing up the abdomen.

The usual practice is not to do a splenectomy if the red cells are below 2 million per c.mm., and only then after a blood transfusion; but in one of our cases, a girl aged 2 years, suffering from Gaucher's disease with an enormous spleen, whose red cell count was just under a million and haemoglobin content 16 per cent., had splenectomy performed forthwith, as her condition was so desperate that she would not have lived for more than a day or two. The child made a perfect recovery, and had a normal blood count after a few months.

Pathogenesis

Much has been written under this heading, but a brief reference will suffice.

Tidy (*British Medical Journal*, December 27th, 1930) stated: "(1) The haemorrhages in the haemorrhagic diathesis are primarily due to increased permeability of the capillary endothelium. (2) Blood platelets normally protect the capillary endothelium, and the diminution in number observed in the haemorrhagic diathesis is secondary to this action." Against these suggestions I would mention that after splenectomy in genuine cases of essential thrombocytopenic purpura haemorrhagica there are usually no further haemorrhages from the same capillaries that bled before the operation; there cannot, therefore, be an inherited or acquired defect in the capillaries. The cause must thus be looked for elsewhere. Against the second point I would like to quote the following case.

A patient of mine suffered from secondary purpura, apparently due to *Streptococcus haemolyticus*, and drawing one's hand across her chest produced a large haemorrhagic area in which occurred the usual changes of colour. I asked Dr. Knyvett Gordon to estimate the platelets in her blood, and then produced haemorrhagic areas on the chest as above stated. After a period of fifteen minutes the blood platelets were again estimated. The result showed that the platelets before and after production of bruises numbered 300,000 each time.

It would be interesting if the above experiment could be checked by another observer; should the observation be corroborated we would have to look for another cause for this form of purpura.

It has for some years seemed to me that the cause of essential purpura haemorrhagica is probably the presence of a toxic substance in the spleen, which affects the permeability of the capillaries and also in some way influences the number of thrombocytes in the blood. In my experience of five cases there have been no purpuric symptoms since the operation, and the thrombocytes, after the immediate initial rise, have settled down at a level of about 150,000 per c.mm. I would again suggest that the cause is probably a toxic substance present in the spleen, and that after splenectomy the toxic agent, which had previously affected the capillaries, enabling blood to penetrate through them and produce haemorrhages, must have been removed with the spleen, as otherwise we should probably see a continuance of the bleeding instead of its cessation. If this hypothesis is correct it would be interesting to try the effect of an extract from one of the excised spleens from an essential thrombocytopenic purpura haemorrhagica case on suitable animals, such as guinea-pigs and rabbits, and observe whether purpura results. Or again, the serum from an

active case of this disease could be injected into an animal and the effect watched. Should purpura result some serum from the same patient could be injected again when the patient has no longer any symptoms of purpura, and the results compared. Would the preserved serum from an active case cause purpura if injected into the patient himself during a quiescent period? A similar experiment could be performed on the splenectomized patient a few weeks after the operation.

It seems not unlikely that the same toxic substance in the spleen is chiefly responsible for the excessive loss of platelets which usually occurs in this type of purpura. The explanation of the long intermissions that not infrequently occur between bleedings is certainly difficult. It might signify that the presumed toxic substance in the spleen is only formed in sufficient amount to cause symptoms under certain suitable conditions, the nature of which is at present obscured. In my cases (1) and (4) a number of witnesses noted that the free bleeding from the gums ceased within a few minutes of tying the splenic vessels; further, the bleeding never returned. This seems to suggest that the toxic substance when formed in the spleen quickly finds its way into the circulation affecting capillaries so that haemorrhages occur. On the other hand, when the toxic substance is no longer poured into the blood stream the tendency of the capillaries to bleed ceases almost at once.

Knyvett Gordon states that in essential thrombocytopenic purpura haemorrhagica he found the appearances markedly uniform. The Malpighian follicles were unaffected, except sometimes for slight thickening of the central artery of the stalk, to which he was not inclined to attribute any special significance. The pulp, however, was crowded with proliferating endothelial cells derived from the lining of the venous sinuses. In addition, he found large multinuclear giant cells in which polynuclear cells and platelets, and in some cases red cells also, were enmeshed.

It is well known that accessory spleens are frequently found in the abdomen, and that occasionally large numbers are present. In our series of cases Maingot found that in thirteen cases of essential thrombocytopenic purpura haemorrhagica in which he did splenectomy four had one spleniculus each, the average size being that of a marble. One case had two, and two cases had three or more spleniculi. In 53.1 per cent. spleniculi were found. A spleniculus was microscoped in one case, and similar pathological changes were evident to those seen in the parent spleen.

Two years ago a surgeon stated before the Clinical Section of the Royal Society of Medicine that he had removed the spleen of a case of acholuric jaundice with excellent result for six months, after which the symptoms recurred. Upon reopening the abdomen he discovered a spleniculus that had grown to nearly full size. This was removed, and although some years have now elapsed no further symptoms of the original disease have reappeared. It would thus seem to be a sound procedure when symptoms of purpura recur after splenectomy to reopen the abdomen and search for an accessory spleen, which, if present, should be removed.

Those of our readers who served in the Near East during the war may be interested to learn that a reunion pilgrimage cruise to Gallipoli and Salonika has been arranged by a committee of ex-servicemen. The cruise will leave Liverpool on May 1st, 1936, returning on May 23rd. Fares will range from 21 guineas, one class only, and calls will be made at Malta, Gallipoli, Salonika, and Istanbul. Full particulars can be had from the joint honorary secretaries, Gallipoli and Salonika Pilgrimage Committee, 3, Shaftesbury Avenue, Chesterfield.