TREATMENT OF THROMBOCYTOPENIC PURPURA*

BY

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Idiopathic thrombocytopenic purpura may be defined as a disease characterized by a prolonged bleeding time and diminished platelet count associated with haemorrhages from mucous membranes and into the skin, the aetiology of which is not known. Before making a diagnosis of idiopathic thrombocytopenic purpura it is essential to determine that no focus of infection and no sensitivity to any drug or food substances are present. The disease may occur in an acute and chronic form, and is liable to spontaneous and sometimes complete remissions. The effects of treatment are therefore difficult to assess. Few observers are explicit as to whether the cases reviewed are acute or chronic.

Many forms of treatment have been advocated. Their number alone suggests that none are specific.

Ascorbic Acid

Vitamin C has recently been used in the treatment of idiopathic thrombocytopenic purpura (Table I). No well-controlled observations on patients who have recovered are available. The patient of Böger and Schröder (1934) was a man, aged 60, who had had no previous haemorrhage,

TABLE I.—*Treatment with Ascorbic Acid*

Authority	No. of Cases	Follow-up	Cured	Failure
Vogt, 1935	2 A	?	2	
Böger and Schröder, 1934 ..	1 A	?	1	
Miller and Rhoads, 1936 ..	4 ?	?	4	
Szent-Györgyi, 1936	7	?		7
Wright and Lilienfield, 1936 ..	3	3-7 weeks		3
Davidson, 1937	3 C	7-10 days		3
Vaughan, 1937	1 C	6 weeks		1
Total	21		7	14

A=acute. C=chronic.

and no control period was observed. Vogt (1935) describes two successful cases. The diagnosis in one was doubtful as genital abnormalities were found; in the other a blood transfusion as well as vitamin C was given; in neither was the rise in platelets marked. Miller and Rhoads (1936) have published a preliminary report in which they claim that in four cases treated with ascorbic acid there was complete relief of symptoms and a rise in platelets. No details are available apart from the fact that in two instances improvement was associated with increased output of vitamin C in the urine. Wright and Lilienfield (1936) and Davidson (1936–7), on the other hand, each record three cases which failed to respond to parenteral treatment with ascorbic acid. Szent-Györgyi and his colleagues (Armentano *et al.*, 1936) and Patek (1936) also state that they have found ascorbic acid valueless. We have had a similar experience in one typical case. Szent-Györgyi (Armentano *et al.*, 1936) has recently isolated from lemon juice and from paprica a substance which he has called vitamin P or citrin; this is not present in orange juice. He has found citrin of value in preventing haemorrhage in vascular purpura—that is, purpura occurring in patients with a normal platelet count though with decreased capillary resistance—but useless in thrombocytopenic purpura. Thanks to the kindness of Dr. Smith and Dr. Macfarlane, who prepared some citrin according to the method of Szent-Györgyi, we were able to test this substance on one patient with thrombocytopenic purpura. Neither the platelet count nor the capillary resistance was improved—in fact, the patient became so ill that transfusion was necessary (see Chart).

CASE RECORD

A married man, aged 34, a tailor, had had crops of bruises for two years and bleeding haemorrhoids for two months. He was admitted to hospital with profuse haemorrhage from the gums following teeth extraction. On examination no physical signs apart from petechial haemorrhages and bleeding gums were found. Blood pressure was 110/60; red cells, 4,100,000 per c.mm.; haemoglobin, 74 per cent.; colour index, 0.9; white cells, 13,000 per c.mm.; platelets, 10,500 per c.mm. The bleeding time (Dukes's method) was five minutes. The Wassermann reaction was negative, the capillary resistance test positive. He developed a septic throat; the gums and remaining teeth were also septic.

Treatment.—On September 10, 1936, 80 mg. of ascorbic acid were injected intravenously; this was continued daily for five days with no significant improvement in the platelet count. Doses of 80 mg. of ascorbic acid were given by mouth daily from September 29 till November 2, when the dose was increased to 160 mg. daily until December 13. From December 22, 1936, till January 26, 1937, *x*-ray treatment to the spleen, totalling 4,500 *r* in fifteen periods, was given without significant improvement. On March 9 40 mg. of citrin were injected intravenously, and the same amount on April 6. Throughout this period, in spite of injections for haemorrhoids, the patient had repeated bleeding per rectum. Sigmoidoscopy showed this to be due to oozing from the whole rectal mucosa. On April 13 the red cells numbered 3,700,000 per c.mm., and the haemoglobin was 46 per cent. He refused splenectomy, and was given a transfusion. The platelet count has never reached a figure higher than 160,000 per c.mm., and has shown considerable fluctuations (see Chart). He had always had a positive tourniquet test, and crops of petechial haemorrhages or larger subcutaneous bruises have occurred spontaneously.

The value of ascorbic acid in thrombocytopenic purpura is certainly open to doubt at present, while that of vitamin P is not proven. Certain German workers (Schiff and Hirschberger, 1937) claim to have isolated a further vitamin, present in sesame oil, which they have called T. This is said to exert a specific effect upon the platelets. Further work is required to confirm their observations.

Internal Secretions and Liver

Repeated, though unsatisfactory, attempts have been made to involve certain internal secretions in the control of the blood platelets. Zondek (1936) treated a case of chronic purpura with thyrotropic hormone, and considered that a rise in platelets from 60,000 to 150,000 per c.mm. was a significant cure. Others have used ovarian extracts. Marzullo (1933) claims success in five patients, but gives no details of control periods or of the actual platelet counts. Since the platelet count rises in Addisonian pernicious anaemia after liver therapy (Nittis, 1930–1) it was suggested that such treatment might benefit thrombocytopenic purpura (Table II). Satisfactory results have been claimed (Mondon, 1928; Holboll, 1929; Jacob and Clapperton, 1930), but the majority of the cases were acute and no satisfactory control period was allowed. Witts (1931) had no success in five chronic cases.

* Read at a joint meeting of the Sections of Pathology and Medicine at the Annual Meeting of the British Medical Association, Belfast, 1937.

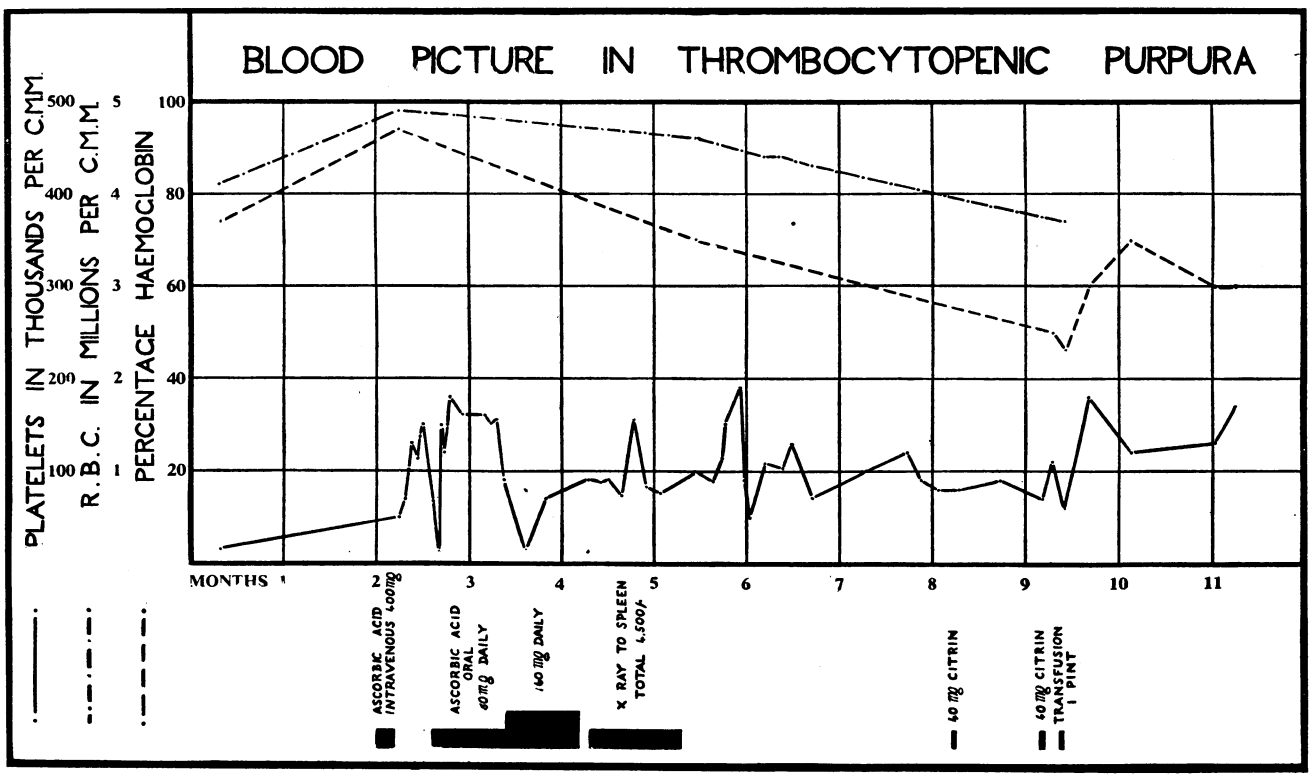
TABLE II.—*Treatment with Liver or Extract*

Authority	No. of Cases	Follow-up	Cure	Failure
Mondon, 1928	1 A	1 month	1	
Holboll, 1929	1 A	3 months	1	
Jacob and Clapperton, 1930 ..	1 C	1 year	1	
Witts, 1931	5 C	2-4 months		5
Total	8		3	5

TABLE III.—*Treatment with Snake Venom*

Authority	No. of Cases	Follow-up	Cure	Failure
Peck and Rosenthal, 1936 ..	32 C	1 month to 4 years	17	15
Lowenburg and Ginsburg, 1936	1 C			1
Jones and Tocantins, 1936 ..	6 C		1	5
Davidson, 1937	3 C			3
Total	42		18	24

The parathyroid gland, because of its effect on the blood calcium, has also been involved. Lowenburg and Ginsburg (1932, 1936) have reported two patients with thrombocytopenic purpura who had failed to respond to treatment with venom and transfusions. Following the production of hypercalcaemia with parathyroid injections all bleeding stopped. In one instance the patient was perfectly well six weeks later, but in neither case did the platelet count return to a figure higher than 290,000 per c.mm. at any time. Mathewson and Cameron (1937) attempted to produce hypercalcaemia with injections of parathormone in one case without any success; neither the platelets nor the blood calcium rose.



Snake Venom

Peck and Rosenthal (1936) claim that repeated injections of moccasin snake venom are extremely successful (Table III). Venom is given subcutaneously. In patients over 10 years old the initial injection is 0.4 c.cm., which is rapidly increased in subsequent injections to 0.8 or 1 c.cm. as a maximum dose. This is usually given twice a week. If symptoms are severe it is given every third day at least. Symptomatic improvement was obtained in seventeen chronic cases, but the platelet count was unchanged. Four cases failed to improve, and in eleven it was necessary to perform splenectomy or ligate the splenic artery. Other workers have failed to obtain any satisfactory result with venom (Davidson, 1936–7; Lowenburg and Ginsburg, 1936; Jones and Tocantins, 1936).

Blood Transfusion

Repeated small transfusions have been thought to accelerate recovery (McLean *et al.*, 1932; Jones and Tocantins, 1933, 1936): 300 c.cm. is regarded as the maximum dose in adults, and is reduced considerably for children. This should be given not less often than every five days, and may be administered daily. Jones and Tocantins (1936) have recently summarized their experience of treating twenty-two patients with transfusions: eight showed permanent improvement, seven temporary improvement, and seven no improvement, and they conclude, therefore, contrary to their former belief, that transfusions are not always effective. These are probably of greatest value in patients who refuse splenectomy or before operation in patients with severe haemorrhage.

X-Ray Treatment

The application of *x* rays to the spleen has been advocated by many observers (Table IV) (Stephan, 1920; Bucky and Guggenheimer, 1922; Gragert, 1921; Hippe and Kochmann, 1932). Many of the early case reports

TABLE IV.—*Treatment with X Rays*

Authority	No. of Cases	Follow-up	Cure	Failure
Stephan, 1920	2 A		2	
Bucky and Guggenheimer, 1922	1		1	
Gragert, 1921	1 A	10 days	1	
Cori, 1922	1	2 months		1
Pancoast, 1925..	{5 C / 1 A}	3 days-3 years		6
Hippe and Kochmann, 1932 ..	7 A	8-40 days	7	
Marzullo, 1933	2 C			2
Mettier, 1936	{6 C / 1 A}	1-7 months	6	1
Rudisill, 1936	7	4 months-4 yrs.	7	
Jones and Tocantins, 1936 ..	6 C			6
Davidson, 1937	3 C	7-14 days		3
Mettier, 1937	1 C	3 months	1	
Vaughan, 1937..	1 C	3 months		1
Total	45		25	20

TABLE V.—*Treatment by Splenectomy*

Authority	No. of cases	Cure	Improved	Operative Mortality	Follow-up	Failure
*Eliason and Ferguson, 1932	213	156	17	13.1%	6 mths. to 5 yrs.	6
Pemberton, 1934	57	36	20	7%	2 mths. to 9 yrs.	1
Williamson, 1934	2				9 years	2
Hartfall, 1934 ..	1	1			6 mths.	
Brown and Elliott, 1936 ..	10	8	1		1 mth. to 11 yrs.	1
Geggie, 1936 ..	6	5			1 month	1
Myers, 1935 ..	1	1			9 years	
Jones and Tocantins, 1936	9	6	3			
Pollok, 1936 ..	1	1			4½ yrs.	
Smith, 1936 ..	1	1			15 mths.	
Davidson, 1937	2	2				
Total ..	303	217	41			11

* These figures include those of previous summaries, notably those of Spence (1928) and Quénu (1929).

show that acute cases were treated, that no control period was given, and that the follow-up was short. Pancoast (1925), who had a follow-up of three years in some instances, reported complete failure in five chronic cases and in one acute case. Interest in this form of therapy has recently been revived by the report of Mettier and his colleagues (Mettier, Stone, and Purviance, 1936; Mettier, 1937). They record success in seven chronic cases. An increase in platelets occurred within twenty-four to forty-eight hours, rising as high as 250,000 to 500,000 within nine days. In some instances relapse occurred one to seven months after the cessation of treatment. Rudisill (1936) concludes from a study of seven patients that Roentgen radiation constitutes an exceedingly valuable and possibly a specific therapeutic agent when applied over the spleen in primary or complicated thrombopenia with haemorrhage. His case records are, however, scanty. We have found, in agreement with Jones and Tocantins (1936), Marzullo (1933), and Davidson (1936–7), that *x*-ray therapy is without effect (see Chart).

Splenectomy

The majority of observers agree that at present splenectomy (Table V) gives more satisfactory results than any other line of treatment in thrombocytopenic purpura. The operation was first performed in 1916 at the suggestion of Kaznelson. Since that time all reviews have shown increasingly satisfactory results, presumably as pre-operative, surgical, and anaesthetic technique improved. Whipple in 1926, reviewing eighty-one cases, found an operation mortality of 16 per cent., a risk which was constant in 1929 when Quénu surveyed 122 cases. Eliason in 1932 observed that the operation mortality had dropped to 13 per cent., while Giffin (1932), reviewing the experience of the Mayo Clinic, found the rate to be as low as 7 per cent., a figure which was present two years later when thirteen additional cases were discussed (Pemberton, 1934). Brown and Elliott (1936) performed ten splenectomies without post-operative disaster. The series of Brown and Elliott (1936) is of considerable interest since eleven untreated cases were used as a control group. Three of the latter recovered completely, but five were unimproved and two were only slightly better. Splenectomy, though it would undoubtedly appear to result in clinical improvement, does not necessarily affect the platelet count except transitorily (Evans, 1928; Spence, 1928; and Brown and Elliott, 1936). There is usually a definite pre-operative rise, though not necessarily to normal figures, followed by a fall, the count being then maintained at a low level. Until recently it has been thought that the operation risk in acute cases was too great to justify splenectomy in fulminating purpura. Whipple (1926) records seven deaths in eight acute cases at operation, Spence (1928) ten deaths in twelve cases. Eliason (1932), however, in twenty-two patients splenectomized during a fulminating attack between 1928 and 1932, found the mortality had dropped to 13.6 per cent., a figure accepted as representative of modern results by Brown and Elliott (1936). Few cases are reported in which the results are satisfactory for the first few months after splenectomy but which subsequently relapse (Williamson, 1934). It appears probable that such relapses are due to the development of a splenunculus, and are by no means an inevitable result of splenectomy. Maingot (1936), who made a careful search for accessory spleens in a series of thirteen cases of splenectomy for purpura haemorrhagica, found them in seven. There are several patients who have remained well for as long as eleven years after operation.

TABLE VI.—*Summary of Treatment Results*

Treatment	No. of Cases	Cured	Improved	Failure
Ascorbic acid	21	7		14
X rays	45	25		20
Snake venom	42	18		24
Liver extract	8	3		5
Hypercalcaemia	2	2		0
Splenectomy	303	217	41	11

The figures reviewed are not necessarily complete, but they are presumably representative. They show cure in 217 cases, improvement in forty-one, and failure in only eleven, apart from those that did not survive operation.

Conclusions

It would appear, therefore, that the chance of curing a patient with thrombocytopenic purpura by the administration of ascorbic acid is, from the evidence at present available, 33 1/3 per cent. There is a rather higher chance that *x* rays may be of value—twenty-five favourable reports against twenty unfavourable have been found. Observations on snake-venom therapy at present show eighteen patients benefited and twenty-four with no improvement. There is no evidence that liver extract is of value. Hypercalcaemia has been tried in too few cases to permit of any conclusion. Transfusion has its greatest value in tiding an acute case over the preliminary stage and in pre-operative preparation. Splenectomy to-day has an immediate mortality rate of 7 per cent. or rather less, and the majority of patients who recover from operation have a reasonable chance of permanent improvement.

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THE NERVOUS FACTOR IN JUVENILE ASTHMA

BY

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An investigation of the known aetiological factors in asthma was undertaken in a large number of cases seen over a period of five years.* The present paper briefly summarizes some of the observations made on the "nervous factor" in 187 of those patients, whose ages ranged from 2 to 20 years.

Evidence was early cumulative to show that the psychological element intruded in a varying degree in almost every case, and it was eventually possible to classify its relation to the syndrome according to three factors: (1) the nature of the inheritance and environment; (2) the degree of allergic thraldom; (3) the duration of the condition.

At an early stage of my investigation I was struck by the fact that a preliminary conversation with the parents of an asthmatic child could enable me to assess with surprising accuracy the measure of success which would attend treatment. Further experience made it increasingly obvious that parental invasion of its psychic life could markedly influence the affective states of the child. As Jung points out, "the first form of a complex cannot be other than a parental complex, because the parents are the first reality with which the child comes in contact." This is of supreme importance to our problem because, as I shall later attempt to show, allergy carries with it certain psychological limitations, and the allergic child is often made aware of disordered emotional currents in its allergic parents, and tends to fashion its own reactions in a "preselected" imagery.

What are the characteristics of those reactions, and how are they related to the syndrome? It is only possible to answer those questions when psychological considerations are related to physiological data.

Disturbance from Biochemical Changes

Analysis of the case histories under review shows that in the great majority the ideational pattern of the affective states is already deeply grooved in the nervous system prior to the onset of asthma. Around a primary nucleus of fear is developed a diffuse background of "oversensitiveness" or apprehension. Clinically, this is evidenced by the fact that stimuli which impinge closely on the emotional life of these children appear to excite a diffuse wave of psychic radiation. The normal reciprocal inhibition is hereditarily faulty. The resultant loss of localization of stimuli widens the horizon of apprehension. The decision about what is to be done becomes momentous; the nature of the child's psychic endowment will be the ultimate guide to that decision. A failure in adaptation or a tendency to false compensation will enhance a potential overflow into autonomic channels. But, in my opinion, at this early stage rarely can emotion pervert the machinery of the lower centres until something of a purely physical nature impairs the integrity of cortico-thalamic control. All the evidence suggests that this disturbance is brought about by biochemical changes ushered in by allergy. In 98 per cent. of my cases I have not been able to determine a purely psychogenic cause for the onset of asthma in the absence of other factors. It must, how-

* "A Review of 300 Cases of Asthma in General Practice." (Sir Charles Hastings Prize, 1936.)