thrombus is rendered temporarily complete by an associated spasm of the remaining veins in the limb. At the same time there may be some degree of arterial spasm as well, and it is these several factors, varying in degree, which give rise to the different clinical varieties.

The condition may well be of medico-legal importance, for the development of gangrene in a limb following operation for varicose veins does not necessarily mean that the main artery or even the main vein has been tied.

Much of the treatment is indicated by the pathology. Heparin should be given to achieve and maintain a clotting-time of 15 to 20 minutes, and associated shock is treated by transfusion and other methods. The affected limb should be elevated to an angle of at least 45 degrees to take the best advantage of gravity, and, if the patient's general condition allows, supervised active exercises should be vigorously pursued.

Veal *et al.* recommended this treatment in all cases, and considered that any sympathetic release should be avoided, as it increases the embarrassment of an obstructed venous system. They also stated that if the condition follows ligation of a main vein the ligature should be removed immediately.

If, however, the argument is accepted that the obstruction to the venous drainage is to some degree functional, then it would appear advisable to try to break this reflex by a method of sympathetic release, and, as I have indicated above, it seems to me that there must be a large measure of spasm, at least in those cases which have a chance of recovery.

In a heparinized patient any sympathectomy by resection or by paravertebral injection is dangerous and very likely to produce a retroperitoneal haematoma, and should therefore be avoided. A quite adequate sympathectomy can readily be achieved by means of heat applied to the trunk and unaffected limbs, liberal doses of alcohol, one of the best available vasodilators, and the induction of deep sleep with soluble amylobarbitone in doses of 3 gr. (0.2 g.) hourly until the patient is difficult to rouse, or liberal doses of morphine if pain is severe. This is a regimen appreciated by patients, and it has the advantage of allaying anxiety, besides achieving its effect on the sympathetic. The affected limb should be kept at room temperature, as should any limb threatened with gangrene, and intra-arterial tolazoline may be tried, although I have not been very greatly impressed with this procedure, and my own preference is for the intravenous route in urgent cases. As soon as the patient is fit enough, the elevated limb should be exercised actively several times a day under the supervision of a physiotherapist. In many cases the swelling resolves, the pain is relieved, and the circulation returns, often rather suddenly, in whole or in part. If return of circulation is incomplete, massive or superficial gangrene may result. Pulmonary embolism is a common danger, but heparinization will tend to prevent this complication. In the event of minor or major gangrene developing, removal of tissue (or amputation) should be restricted to the dead part, since the circulation in the surviving proximal segment has always completely recovered before the need for ablation of dead tissue arises.

Summary

The association of acute ischaemia or even gangrene with thrombophlebitis of the extremities is discussed, and the name phlegmasia caerulea dolens is considered to be adequately descriptive.

The different clinical manifestations are described.

The mechanism of the ischaemia is considered, and a theory advanced to account for the varieties.

Treatment is described in outline.

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SURVIVAL OF TRANSFUSED RED CELLS IN SCURVY

BY

C. MERSKEY, M.D., M.R.C.P.

Department of Medicine, University of Capetown

The pathogenesis of the anaemia of scurvy is obscure. One view is that the mechanism may be inadequate haemopoiesis due to deficiency of vitamin C. Vilter *et al.* (1946) and others have suggested that there may be a haemolytic process.

The theory of haemolysis has been based on the occurrence of reticulocytosis and abnormally high serum bilirubin and faecal and urinary urobilinogen values in patients with scurvy and anaemia. These findings are not necessarily due to haemolysis. A more reliable indication may be obtained by studying the fate of transfused red cells. As search of the literature has not revealed any report of such an investigation in scorbutic patients, studies of the survival of transfused cells have been made in eight patients with scurvy and anaemia and in one with scurvy but without anaemia.

In six of these patients the transfused red-cell survival time was greatly reduced, and this was interpreted as evidence of a haemolytic process.

Material and Methods

Eight adult male patients (seven Bantu and one Indian) who manifested severe scurvy and anaemia with normoblastic bone marrow have been investigated. The ninth patient, an adult male Bantu, was scorbutic but not anaemic. For some time before admission to the Groote Schuur Hospital these patients had been on a diet severely deficient in vitamin-C content, consisting almost solely of mealie meal (maize) and white bread. All presented the classical picture of scurvy, with spongy haemorrhagic gums, follicular hyperkeratoses, and intramuscular haematomata. There were no signs of any other disease.

The investigation of the eight anaemic cases was divided into four stages as follows:

(1) Initially the patient was kept at complete rest in bed, without any medication and on a diet entirely lacking vitamin C (mealie meal porridge without milk or sugar, stamped mealies, white bread without butter or jam, and black tea and coffee).

(2) After the short control period of rest in bed, the patient was given one transfusion of citrated bank blood which had been stored for at least 36 hours. Between 2 and 4 pints (1.1 and 2.3 litres) of blood were given in each case according to the degree of anaemia. The vitamin-C content of the blood used in each transfusion was not determined, but the average vitamin-C content of 8 pints (4.5 litres) of blood, taken and stored for 36 hours under the same conditions

as the transfused blood, was found to be 1.45 mg. per 100 ml. The vitamin-C-free diet was maintained during this stage.

(3) Between 8 and 18 days after transfusion the patient was given by intramuscular injection 500-1,000 mg. of ascorbic acid daily for a period of 6-10 days while still receiving the vitamin-C-free diet.

(4) Finally, the patient was given a full diet.

In Case 5 the investigation had to be curtailed because he developed chest pain, possibly due to pulmonary embolism. He was therefore given vitamin C on the third post-transfusion day.

In the non-anaemic patient a blood transfusion was given on the day of admission to hospital without a preliminary period of observation. He was investigated for six days thereafter whilst kept in bed on the vitamin-C-free diet without any other medication. On the seventh day he demanded his discharge. He was given 1,000 mg. of ascorbic acid intramuscularly and a full diet; he was subsequently seen as an out-patient.

The red-cell survival times were determined by the Ashby technique, using potent anti-A and anti-B sera (Mollison, 1951). In Case 6, with blood group O, powdered anti-M serum in the form of powdered globulin was used. The estimations of survival times were made either daily or on alternate days. In Cases 2 and 3 the estimations were made on capillary blood. In the other seven cases venous blood was used. In each estimation at least 2,000 cells were counted.

Whilst the patients were on the control diet every possible precaution was taken to prevent them from receiving extraneous sources of vitamin C, apart from the ascorbic acid given by injection and the small quantity in the transfused blood. In error Case 6 was given a glass of sour milk on the sixth day after transfusion, but no other breach of the strict dietary control is known to have occurred.

No other medication was given at any stage except that Case 4 received one injection of 25 mg. of A.C.T.H. on the 18th day after transfusion for the purpose of testing adrenocortical function. This patient bled severely on that day and was immediately given a second blood transfusion; in all other cases only one transfusion was given. As part of another investigation four cases (Nos. 2, 5, 7, and 9) received an intravenous injection of the sodium salt of *para*-aminohippurate; in addition Cases 2 and 5 received an injection of sodium thiosulphate, whereas Cases 7 and 9 were given inulin.

Results

The Table shows blood findings in each patient before and after transfusion, before vitamin-C therapy, and on discharge. Figs. 1 and 2 show the red-cell survival times for the nine cases.

In Cases 2, 5, and 8 the red-cell survival could not be regarded as being abnormal. In Case 2 the survival-time curve was normal except that the red cells seemed to disappear rapidly at a stage one week after the beginning of vitamin-C therapy. Cases 5 and 8 were followed for only three and six days respectively before being given vitamin C.

In the remaining six cases (Nos. 1, 3, 4, 6, 7, and 9) the transfused red-cell survival times were much shortened. The effect of administering vitamin C in these six cases was as follows. In Cases 3, 6, and 7 the abnormal degree of red-cell destruction diminished coincidentally with the administration of ascorbic acid as indicated by the flattening of the red-cell survival curves. In Cases 1 and 9 the increased rate of destruction persisted for two to three days after ascorbic acid therapy was started. Case 4 was investigated for 18 days before ascorbic acid was given. On the 18th day he bled severely from nose, mouth, and gums, and required a second blood transfusion. An injection of 25 mg. of A.C.T.H. had been given on that day to assess adrenocortical function. The increased rate of disappear-

FIG. 1.—Red-cell survival curves for Cases 2, 4, 5, 8, and 9. Case 4 received two transfusions. The arrow indicates the beginning of treatment with ascorbic acid.

Blood Findings

	Case 1		Case 2		Case 3		Case 4, a		Case 4, b		Case 5		Case 6		Case 7		Case 8		Case 9	
	Hb %	Trans-fused Cells %	Hb %	Trans-fused Cells %	Hb %	Trans-fused Cells %	Hb %	Trans-fused Cells %	Hb %	Trans-fused Cells %	Hb %	Trans-fused Cells %	Hb %	Trans-fused Cells %	Hb %	Trans-fused Cells %	Hb %	Trans-fused Cells %	Hb %	Trans-fused Cells %
Before transfusion ..	54	0	38	0	80	0	72	0	41	24	51	0	51	0	22	0	90	0	30	0
After ..	64	100	66	100	97	100	68	100	73	100	76	100	91	100	56	100	105	100	53	100
Before vit. C ..	63	49	89	80	104	44	61	24	—	—	79	89	58	60	39	54	100	122	43	41
Last observation ..	89	37	96	30	98	36	—	—	95	62	85	102	88	35	67	38	100	107	82	21
Day vit. C started ..	10		13		13		18		0 (18)		3		10		10		6		8	
Day of last observation	28		25		22		—		25 (44)		8		30		34		12		22	

ance of the donor cells continued after haemorrhage ceased, and the red-cell survival curve did not flatten until 9–10 days after the beginning of ascorbic acid therapy.

Haemoglobin values were determined in each case *pari passu* with the estimation of volume of packed red cells.

Of the six cases in which there was rapid disappearance of donor cells, four (Cases 4, 6, 7, and 9) showed a fall of haemoglobin simultaneously with the decrease in volume of packed red cells, whilst in Cases 1 and 3 the haemoglobin did not drop below the immediate post-transfusion level. It is noteworthy that in Cases 4 and 9 the fall of haemoglobin and packed cell volume occurred despite a great increase of reticulocytes.

FIG. 2.—As for Fig. 1. Cases 1, 3, 6, and 7.

Of the three cases (Nos. 2, 5, and 8) in which the red-cell-survival times were found to be normal, the one which could be followed adequately (Case 2) had haemoglobin above the post-transfusion level. In this patient there was a marked reticulocytosis on the day of transfusion and for several days thereafter. This could be attributed perhaps to rest in bed or possibly to some intake of vitamin C a few days previously of which no history could be obtained. The degree of anaemia in Cases 2 and 5 before transfusion was as severe as that of patients in whom the red-cell survival was very much reduced.

All the patients were Rh-positive. The direct and indirect Coombs tests were negative in every case. All recovered completely and were discharged from hospital feeling well.

Comment

It appears that at least in some cases of scurvy with anaemia there is an abnormally rapid rate of disappearance of transfused red cells.

The phenomenon of excessive rate of disappearance of donor cells may be due to either haemorrhage or haemolysis. In the six cases described above in which transfused red cells disappeared rapidly there was no haemorrhage to account for this. The gums were haemorrhagic, but the loss of blood from this source is negligible, as the tests for occult blood in the stools were almost invariably negative. In Case 4 there was considerable haemorrhage, but the disappearance of donor cells had been excessive prior

to this, and continued to be excessive even after haemorrhage ceased. The patients had intramuscular haematomata, but these did not seem to increase in size after transfusion. This is not a matter on which one can dogmatize, since the haematomata were not measured. The shortened survival time of red cells seemed to be due to haemolysis.

Pigment studies, such as the measurement of stool and urine urobilinogen excretion, were not made in these patients. Bronte Stewart (1950, 1953) studied a similar group of patients with scurvy and anaemia in this hospital who were not transfused. He found that their urobilinogen excretion was greatly increased above normal values. This was related in large degree to the presence of intramuscular haematomata. He was unable to interpret his findings as providing positive evidence of an intravascular haemolytic process, although the occurrence of such haemolysis could not be excluded with certainty.

The course of the anaemia of scurvy patients who are merely put to rest in bed, without any other therapy and while still receiving a vitamin-C-deficient or vitamin-C-free diet, is important in this discussion. Other workers have reported observations on this point. In a few cases there has been spontaneous remission of the anaemia (Ungley, 1938; McMillan and Inglis, 1944; Vilter *et al.*, 1946). In the majority the anaemia has remained stationary (Mettier *et al.*, 1930; Ralli and Sherry, 1941; McMillan and Inglis, 1944; Vilter *et al.*, 1946).

In occasional cases there has been a rapid increase in the degree of anaemia despite increased reticulocytosis (Mettier *et al.*, 1930; Jennings and Glazebrook, 1938; Vilter *et al.*, 1946; Bronte Stewart, 1950; Brown, 1951).

It is not clear why there is this variability of course of the anaemia on rest in bed alone. Pirani (1952) has shown that small but significant amounts of ascorbic acid are present in the adrenal glands and other tissues even in the most advanced states of scurvy. It is possible that rest in bed might promote remission of the anaemia by diminishing the general metabolic demand for vitamin C and thereby making the tissue vitamin-C reserves available for erythropoiesis. Whether or not this will occur might depend on the ratio of the amount of vitamin C available to the amount required.

Such a balance mechanism might account for the extremely rapid disappearance of donor red cells in so many cases in this investigation, because the large transfusion of blood increases the general metabolic demand for the inadequate amount of available tissue vitamin C.

The speed with which donor cells were eliminated and the rapid fall in the patients' haemoglobin appeared to be in excess of the fall in haemoglobin observed by other authors in patients who had not been transfused and who had been kept in bed on a vitamin-C-free diet.

Thus, whilst the results of this investigation support the view that there is a haemolytic factor causing diminished survival time of red cells transfused to scurvy patients, they do not necessarily indicate that a haemolytic process is the cause of the anaemia in untreated cases. Further investigation to elucidate this point is planned.

It is curious that the abnormally rapid rate of red-cell destruction appeared to persist in three cases for some days after vitamin-C therapy was begun. It is possible that the cells were "prepared for destruction" and could not be saved by the treatment. Alternatively, it is possible that the haemolytic mechanism persisted for some days owing to some tissues having a prior claim to the added vitamin C.

Summary and Conclusions

Eight cases of scurvy with anaemia and one without anaemia have been observed whilst at rest in bed on a vitamin-C-free diet. Transfused red-cell survival times were determined in each case and found to be abnormally short in six of the nine patients. In three of these six patients the increased rate of red-cell destruction

persisted for some days after the beginning of vitamin-C administration. In the remaining three of the nine patients the donor red-cell survival times appeared to be normal, but two of these cases could not be studied adequately, and even the one who was adequately followed showed a rapid fall in the number of transfused red cells one week after vitamin-C therapy was started. It is possible that the blood transfusion materially increased metabolic demands for vitamin C, and this factor may have contributed to the rapid destruction of donor cells. With this reservation, the results of this investigation support the view that a haemolytic process is an important factor in the pathogenesis of the anaemia of scurvy.

ADDENDUM.—Since this paper was prepared an additional nine Bantu male patients with scurvy and normoblastic bone marrow have been studied by the same methods. Three of these, who were severely anaemic, were transfused with sedimented red cells from 1 pint of blood. All three patients eliminated the transfused red cells very rapidly. In the remaining six patients 1 pint of blood was first removed; subsequently they were transfused with 1 pint of blood. Red-cell survival was greatly decreased in five of these patients, the sixth patient having a normal red-cell survival time. The sixth patient (and one of the five with diminished red-cell survival) was not anaemic. The other four were anaemic. It appears that the proviso inserted in the main body of the paper that overtransfusion might be playing some part in the abnormal red-cell survival in untreated scurvy is unnecessary. Red-cell survival was abnormal even when a replacement transfusion was substituted for simple transfusion. An increase in the protein content of the diet by the addition of thoroughly stewed meat also did not alter the diminished red-cell survival in the last four patients studied. In the combined series there were thus 14 anaemic patients and 2 non-anaemic patients who were maintained on the vitamin-C-free diet for more than seven days. Of the anaemic cases 13 had greatly diminished red-cell survival. Of the non-anaemic cases, red-cell survival was normal in one and diminished in the other.

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The Association of Universities of the British Commonwealth has published a useful list of postgraduate fellowships, scholarships, grants, etc., for advanced study and research, tenable at universities in the United Kingdom, together with details of some of the more important awards tenable overseas by British graduates. The list is published by the Association at 5, Gordon Square, London, W.C.1. Academic interchange between the universities of Britain and those of other European countries has been sponsored by the British Council for several years. The Council has now published a pamphlet (*University Interchange between the United Kingdom and other European Countries, 1948–1953*) listing all such interchanges.

CEREBELLAR NECROSIS IN A CASE OF SUBARACHNOID HAEMORRHAGE

BY

A. L. WELLS, M.D., M.R.C.P.I., D.C.P.

From the Institute of Pathology, Queen's University, Belfast

The possible dangers from lumbar puncture to patients with increased intracranial tension are well known. The main one is forcible impaction—"coning"—of the brain-stem and cerebellum into the foramen magnum, following excessive and rapid drainage of cerebrospinal fluid from the lumbar theca. This may or may not be accompanied by uncalled herniation through the tentorium cerebelli. These risks are mentioned only briefly in the standard neurological textbooks, but their mechanisms have received some close attention in the literature (Jefferson, 1938; Cairns, 1939).

A less frequently cited complication is the precipitation of cerebral haemorrhage, and Schube and Raskin (1936) mention 14 examples occurring in the literature. Two of these were cases of cerebral aneurysm. Androp (1939) reports a case in which death occurred, following lumbar puncture, from haemorrhage into the spinal cord and brain-stem.

Necrosis of the cerebellar tonsils was present in the following case of subarachnoid haemorrhage due to rupture of a cerebral aneurysm. Lumbar puncture was performed three times in the course of the illness. This necrotic lesion is considered to have resulted from an extreme and possibly prolonged degree of coning of the cerebellum. So far as I am aware, such a lesion has not been described before.

Case History

A 41-year-old housewife was admitted in an unconscious state to a country hospital in Northern Ireland on November 14, 1951. She had complained of headache since November 9, and had collapsed on the 13th. On examination there was pronounced neck stiffness, and a subhyaloid haemorrhage was present below the right optic disk. At lumbar puncture the fluid was blood-stained and under obviously greatly increased pressure. The supernatant fluid was xanthochromic.

The patient's condition improved somewhat until November 17; she was more conscious, but now complained of diplopia, although an external ocular paresis could not be demonstrated. On the 19th lumbar puncture was repeated, and yellow fluid not under increased pressure was obtained. Following this, she complained of headache, and became drowsy. A right lower facial weakness was noticed at this time.

Again there was some improvement, and on November 24 lumbar puncture was performed for the third time. A few drops of clear fluid, not under pressure, were obtained. In a matter of minutes she became shocked and lapsed into semicomatose.

The patient was transferred to the neurosurgical unit at the Royal Victoria Hospital, Belfast, where she arrived at midnight of the same day. She was deeply comatose on admission, with marked neck stiffness, extensor plantar reflexes, and B.P. 150/80 mm. Hg. The pupils were unequal, and fixed in dilatation. Papilloedema was not thought to be present. X-ray examination of the skull failed to reveal any fracture, and the pineal gland was not visible.

Operation was undertaken immediately. In view of the previous right-sided signs, a left temporal burr-hole was made under local analgesia. The dura was found to be