with the following results. The figures indicate survivors after 30 hours.

Test Dose	Control	British T.A.B.	T.A.B. Castellani	T.A.B.Te.
2 m.l.d. ..	0/5	3/4	4/4	3/4
5 m.l.d. ..	0/5	3/3	2/3	1/3
10 m.l.d. ..		3/3	0/3	0/3

Investigation revealed that the mouse in the British T.A.B. series which died after 2 m.l.d. was a weakly and emaciated specimen that should not have been included in the test.

These results show that, whereas the British T.A.B. vaccine is of the standard normally attained by vaccine made from strains rich in Vi antigen, the Italian vaccines have the limited protective power of a vaccine made from non-virulent strains. Owing to a shortage of mice it has not yet been possible to test the German vaccine, of which supplies have only recently been obtained.

Conclusion

In the absence of any other explanation—and it has been impossible to think of any other which would fit the case—it appears justifiable to conclude that the relative immunity to enteric fever enjoyed by British troops in captivity is attributable to the use of a potent vaccine. Similar immunity is not enjoyed by the Axis Forces, who seem to have a high endemic rate, and among whom an outbreak of considerable magnitude occurred despite inoculation with vaccine of Italian manufacture.

FAMILIAL IDIOPATHIC METHAEMOGLOBINAEMIA

WITH A NOTE ON THE TREATMENT OF TWO CASES WITH ASCORBIC ACID

BY

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Lurgan

It has been known for some time that ascorbic acid is related to haematopoiesis in human beings. The nature of the association is not clear. Dunlop and Scarborough (1935) showed that a rise in the number of red blood cells, a fall in reticulocytes, and an increase in haemoglobin followed when vitamin C was given to a patient suffering from scurvy, although the iron content of the diet was unchanged. Barron and Barron (1936) observed that ascorbic acid reduced the red cell count in rabbits suffering from polycythaemia induced by cobalt poisoning. It was thought that polycythaemia is caused by inhibition of the respiration of immature red blood cells and their expulsion from the bone marrow into the circulation as mature non-respiring cells. Kandel and LeRoy (1938) treated two cases of polycythaemia vera with large doses of ascorbic acid without altering the red cell count or haemoglobin level.

Hawley *et al.* (1936) found that sodium bicarbonate raised the renal threshold for ascorbic acid and reduced the amount excreted. In an investigation of the ascorbic acid metabolism in two cases of polycythaemia (Deeny, 1940) it was found that a comparatively low level in the blood was accompanied by the excretion of appreciable amounts of ascorbic acid. On raising the threshold with sodium bicarbonate, large doses of ascorbic acid caused clinical improvement in the two subjects. Impressed with these results, we believe that this treatment might correct a defect in a function of the red blood cells occurring in polycythaemia. One of us (J. D.) observed its beneficial effect in cases in which cyanosis indicated difficulty in maintaining a sufficient supply of oxygen to the tissues—as in congenital heart disease. Clinical changes characterized by improvement in the cyanotic colour and alleviation of symptoms occurred, but the results were somewhat inconclusive and difficult to measure accurately. In a search for subjects in whom objective changes could be demonstrated two cyanosed brothers were discovered who proved to be suffering from familial idiopathic methaemoglobinaemia.

Case I

A clerk aged 29 had been a livid blue colour since birth. There was no history of previous occurrence of the condition in his family. One brother (Case II) was cyanosed. His father, mother, two other brothers, and a sister were healthy and normal. The father died recently from cardiac disease, and a brother from whooping-cough at 6 months. The present subject had had measles, whooping-cough, scarlet fever, and chicken-pox in youth, and lobar pneumonia two years ago. He was in the Royal Victoria Hospital, Belfast, for three weeks in 1933, under Dr. R. Marshall, for investigation, and as a result of spectroscopic blood examination a diagnosis of methaemoglobinaemia was established. No cause for the condition was found, and treatment with potassium permanganate enemata did not improve him.

When we first saw the patient he stated that he felt moderately well, but was very constipated, and breathless on exertion. He could not take strenuous exercise, and noticed that his condition became more pronounced in cold weather. He was keenly aware of his colour, and as a consequence had become rather "nervous." On examination the skin of the face—including the ears and neck—the hands, feet, mucous membranes, and to a lesser extent the trunk, were a deep bluish colour. In contrast to the cyanosis usually found, there was no underlying reddish tint. The skin of his face was coarse and thickened. He was of medium height and slight build, and was moderately nourished. His heart was normal in size and rhythm, and no valvular defects were observed. B.P. 140/90; R.B.C. 5,900,000; spleen not palpable. Haemoglobin estimations carried out with the Dare haemoglobinometer were not satisfactory owing to the abnormal pigment present. The chest was moderately developed, but expansion was poor. No abnormality was found on percussion or auscultation. Mild dyspnoea was noted on exertion. All deep and superficial reflexes, and co-ordination and sensation, were normal. The tongue was moist, with white fur on a blue background; the fauces were congested. The abdomen was normal. Urine examination did not reveal the presence of any reducing or other abnormal substances. An estimation of the oxygen-combining capacity of his blood was carried out by means of the Barcroft method, and was found to be 13.2 vols. per 100 c.cm. (normal, approximately 20 vols. per 100 c.cm.).

Treatment was begun on March 30, 1942. He was given 50 mg. of ascorbic acid night and morning by mouth on the first day, then 100 mg. similarly the next two days, followed by 150 mg. twice daily thereafter. Sodium bicarbonate (2 drachms) was given each day at noon. On the eighth day, when he had taken a total of 2 g. of ascorbic acid, a sudden and noticeable change occurred in his colour, and on the twelfth day his complexion became natural. Since then he has continued with 300 mg. of ascorbic acid and 1 drachm of sodium bicarbonate a day, and has remained normal in appearance. The ascorbic acid was given in graduated doses, as it was uncertain what might result from any possible rapid increase in available oxygen. In this respect the only significant feature was a sudden attack of vertigo on the third day of the treatment, which lasted for 30 minutes, but passed off without ill effect. After one month the oxygen-combining capacity of his blood was 22 vols. per 100 c.cm.

Case II

A shop assistant aged 19. The condition was possibly present at birth, though only to a slight extent; but it became much more pronounced at the age of 11 years. He is not so deeply cyanosed as Case I, is much more strongly built, is athletic, and plays hockey for the local team.

The dramatic change in Case I brought about by the treatment was of such interest that the two men were shown to Profs. H. Barcroft and D. C. Harrison of Queen's University, Belfast, and Profs. J. M. O'Connor, E. J. Conway, and F. Kane of University College, Dublin. As a result it was arranged that Profs. Barcroft and Harrison and Dr. James McMurray should carry out certain investigations during the course of our treatment of Case II. (Details of these investigations will be

published elsewhere.) The following is a brief summary of their report:

The diagnosis of methaemoglobinaemia was confirmed by spectroscopic examination of the chocolate-coloured blood. This diluted blood showed an absorption band in the red waveband 632–634 mμ, which disappeared on adding ammonium sulphide. Sulphaemoglobin was absent. The methaemoglobin was intracorpuscular.

Case II was seen before treatment and about a dozen times after treatment began. The aim of each visit was the collection of data on the following: (1) The colour of the skin. Objective records were made by an experienced artist, who painted strips of canvas to match chosen spots on the head and hands. (2) Subjective symptoms. (3) The blood ascorbic acid by Deeny, Murdock, and Rogan's (1942) method. (4) The percentage of the total blood pigments in the form of methaemoglobin calculated from: (*a*) the oxygen-combining haemoglobin by Peters and van Slyke's (1932) gasometric method; (*b*) the total blood pigments by Rimington's (1942) method standardized with blood of known haemoglobin content (Peters and van Slyke's (1932) gasometric method). All determinations were done in duplicate. Some of the results were checked by an independent spectroscopic method. (5) The R.B.C. count. (6) The reticulocyte count.

Treatment began on the evening of May 4, 1942, with 100 mg. of ascorbic acid b.d.s., morning and evening, and 1 drachm of sodium bicarbonate at midday. On the evening of May 20 the dose of ascorbic acid was doubled. During the first month a striking change occurred in the patient's appearance. The slate or battleship blue of his lips and ears gradually disappeared, yielding to the normal reddish tones. The strips of canvas of the tint of the ear-tip, for instance, showed the gradual transition from blue-black to normal beyond any question. He felt great satisfaction that his appearance was now normal. Strenuous exercise was less exhausting.

The blood changes are summarized in the following table. The initial whole-blood ascorbic acid was 0.19 mg. per 100 c.cm. During treatment it rose eightfold in 3 weeks and became stabilized at a level of about 1.73 mg. per 100 c.cm.

Date	Blood Ascorbic Acid mg./100 c.cm.	Total Blood Pigments g./100 c.cm.	% Hb as MetHb	R.B.C. millions/ c.mm.	Reticulocytes per cent.
4/5/42	0·19	16·9	43		
100 mg. vitamin C b.d.s., and ʒi sodium bicarbonate given daily:					
7/5/42	0·29	17·7	40	5·8	
10/5/42	0·46	17·5	30	6·2	5·5
13/5/42	0·68	17·7	28		4·2
16/5/42	0·94	18·9	19	6·1	2·5
20/5/42	1·58	17·3	17	6·0	
200 mg. vitamin C b.d.s., and ʒi sodium bicarbonate given daily:					
23/5/42	1·64	16·5	15		
28/5/42	1·75	16·7	12	5·2	0·5
4/6/42	1·73	14·4	6	5·3	<0·5
30/6/42	1·72	13·7	6	4·4	
13/1/43	1·52	14·75	9·5	5·2	0·25

During the first month, as might be expected from the disappearance of the cyanosis, the proportion of abnormal pigment fell sharply from 43% to 6%. After two months it was still 6% (0.8 g. methaemoglobin per 100 c.cm. of blood). The red cell and reticulocyte counts fell decidedly. This may have been due to the subsidence of a mild secondary polycythaemia stimulated by the diminished oxygen-carrying power of the blood.

The following observations were made on Case I on June 1, 1942, the 63rd day of treatment: blood ascorbic acid, 1.55 mg. per 100 c.cm.; 11% methaemoglobin (sulphaemoglobin absent); R.B.C., 5,080,000; reticulocytes, 0.5%.

Comment

These are the first cases of familial idiopathic methaemoglobinaemia described in Great Britain and Ireland. Abroad the disease has been definitely established in two families, and questionably in another two. Bensley, Rhea, and Mills (1938) reported cases in a brother and sister in Canada, who first became blue at the age of about 11. Their blood contained 5 to 10% of methaemoglobin. An interesting point was that the sister had eight normal children. Lian, Frumusan, and Sassier (1939) reported two brothers in France blue-black from birth with a 35 to 45% blood methaemoglobin, while three other brothers and one sister were alive and normal. A brother and two sisters—said to have been blue—died young. Both brothers had an increased red cell volume and a diminished liver function, which may have been signs of other hereditary abnormalities.

Hitzenberger (1932) reported the case of a mentally defective dwarf, aged 23, a "schwerarbeiter," born blue; 40% of his haemoglobin was in the aberrant form. There was a family history of two mentally backward dwarf brothers, who had died aged about 20, and who were said to have been blue. The cause of death was unknown. Another probable familial case was that of van Thienen (1933)—a woman aged 33, born blue, otherwise healthy. Her father was said to have been blue, but this could not be verified. Isolated cases of what was probably idiopathic methaemoglobinaemia have been described by Miller (1930), Dieckmann (1932), van Lier (1933), and Leiner and Minibeck (1935).

Those suffering from the disease usually have little or no physical disability, and first seek treatment for some other complaint. The blue colour usually dates from birth. Congenital heart disease is often suspected. Physical examination shows nothing abnormal in the cardio-pulmonary system. A sample of blood is then taken for examination for abnormal blood pigments. The blood is a dark chocolate shade which persists after it has been aerated. The spectroscope shows methaemoglobin. Methaemoglobin may of course appear in the blood for other reasons. Bensley, Rhea, and Mills (1938) classify methaemoglobinaemia as toxic, haemolytic, enterogenous, or idopathic. The toxic form follows the excessive use of acetanilide, antipyrine, phenacetin, etc. The abnormal pigment usually disappears 24 to 72 hours after discontinuing the drug. The haemolytic form may occur in infection by anaerobic bacteria, in eclampsia, in blackwater fever, etc. The plasma contains methaemoglobin. Enterogenous methaemoglobinaemia (intracorpuscular) occasionally accompanies severe diarrhoea.

At the time we began treatment of the two blue brothers we were unaware of Lian, Frumusan, and Sassier's (1939) paper, in which they describe the treatment of one of their cases with 100 mg. of ascorbic acid intravenously, daily for three weeks. They tried vitamin C because from the chemical relationship of methaemoglobin to oxyhaemoglobin it seemed possible that ascorbic acid might convert the former directly into the latter. A free translation of their conclusions reads: "It is absolutely certain that this therapy has been followed not only by complete disappearance of the functional symptoms (dyspnoea and headache), not only by sensation of well-being, of euphoria, but by remarkable diminution in the abnormal colour. At the same time the proportion of the pathological pigment dropped from 45 to 26% of the total quantity of haemoglobin. . . . An interruption of 10 days in the ascorbic acid treatment has been followed by a marked aggravation of the cyanosis and a rise from 26 to 35% in the blood methaemoglobin." They have not recorded any further attempts to treat the condition.

We have now observed the effects of treatment on our two subjects for a period of one year, and during that time both have had improved health and normal complexions.

Summary

Two cases of familial idiopathic methaemoglobinaemia are described.

This is the first time this very rare disease has been reported in Great Britain and Ireland.

A permanent blue colour of the skin, usually dating from birth, is sometimes the only symptom.

The findings of Lian, Frumusan, and Sassier (1939) that administration of ascorbic acid diminished cyanosis and methaemoglobinaemia are confirmed.

In our cases the skin colour became normal a few weeks after beginning daily doses of vitamin C and sodium bicarbonate by mouth. In one case methaemoglobin in the blood fell from 43 to 6% at the end of the fourth week of treatment. The change has been maintained in both cases for one year.

We wish to thank the Medical Research Council of Ireland for assistance; Profs. Barcroft, Harrison, and their associates in Queen's University, Belfast, for the effort and labour which their participation

in this work entailed; and Profs. O'Connor, Conway, and Kane, University College, Dublin, Dr. James McMurray and Dr. Robert Marshall, Belfast, for their interest, advice, and help.

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A NEW METHOD OF GRAFTING

BY

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In order that the principles of the new method may be understood it will be useful first to give a short review of the usual types of skin graft. According to the thickness of the graft four types will here be considered: (1) the thin Ollier-Thiersch graft, which has been described—not quite accurately—as only epidermic; (2) the intermediate or split graft, which contains the whole epidermis and a portion of the dermis; (3) a thicker graft of about three-quarters of the skin, which leaves just enough epithelial elements from the sweat and sebaceous glands for the epithelization of the donor area; (4) the whole-thickness skin, or Wolfe, graft.

In the main, two considerations regulate the choice of graft: the thicker the graft the better the quality of the skin obtained; and the thinner the graft the easier it "takes." The area from which the graft is taken should epithelize in less than 15 days if the graft is thin. In thick grafts epithelization may be retarded, and subsequently some scar reaction may spoil the site for further use as a donor area. In the Wolfe graft there is a complete loss of skin, which must be replaced. It will be seen, therefore, that the donor area has its limitations. The kind of graft to be used depends, too, on the local condition of the area to be grafted and on the general condition of the patient, and is not an easy matter to decide upon. One of the chief problems arises when the area to be grafted is very big and the donor area is limited. When the donor area available is small, or the local and general condition of the patient is poor and none of the above-mentioned grafts is considered advisable, use is often made of small rounded grafts, of which there are two types: the thin or Reverdin graft, and the thick or deep graft devised by Davies and commonly called the "pinch" graft. Both are obtained by the same technique. The latter is the one generally adopted in England.

The Pinch Graft

It is necessary to review the pinch graft for the better understanding of this article. It is usually a small graft (3 to 5 mm. in diameter), rounded, deep, and containing all the layers of the skin. To obtain it a needle is used to pick up a cone of skin, which is cut at its base with a knife. The same needle carries the graft to the recipient area. Usually the pinch graft "takes" in raw areas in which no other graft will properly do so. This is why it is so useful. Moreover, it is easy to carry out. Many reasons are given to explain why the pinch graft takes so easily. In my opinion, the main reason is that the grafts are so placed that enough room is left between them to allow of free discharge, and nothing intervenes between the graft and the recipient area. This is an application of the well-known principle of general surgery that no infected area will heal unless there is ample room for the discharge to escape.

From this consideration there arises a conclusion that is one of the main supports of the new method of grafting: *any graft will take more easily, and in poor raw areas, if there is enough room for discharge inside the whole area grafted.* Certainly, then, pinch grafts have many advantages, yet they have several very important disadvantages.

Disadvantages of the Pinch Graft.—(*a*) The donor area of a pinch graft is practically always spoiled as a further donor area for other types of graft. Numerous small scars or keloids are very common. (*b*) A big donor area is necessary if the pinch grafts are placed very close together—sometimes as big as the area to be grafted. (*c*) It is necessary to employ a large number of them, which may prove to be a very long and tedious job. (*d*) Because, through the instruments, contact is established between donor and recipient areas—very often slightly infected—infection may develop in the donor area. (*e*) Usually the site covered by pinch grafts consists of the good skin of the original pinch grafts surrounded by an area of fairly good skin; the rest is more or less keloidal tissue, in many cases with all the disadvantages of scar tissue.

The Ideal Graft.—It seems to me that if the pinch grafts were placed so close together that the distance between them was less than the possible easy spread of the grafts (from 6 to 9 times the original size of the pinch graft), the likelihood of the formation of good skin and quick epithelization would be much greater. Only experience can confirm this. If I am correct in my assumption, therefore, the ideal graft for the type of case mentioned must conform to the following rules:

1. Plenty of room must be left between the grafts for possible discharge.
2. The donor area must not be spoilt, so that it could be used again and again.
3. The graft should take easily—as well as or better than any other graft.
4. The technique must be fairly rapid in use and the number of grafts unlimited.
5. Contact, direct or indirect, must be avoided between donor and recipient areas.
6. The space between the grafts must be less than the possible easy and early spread of the epithelium.

Technique of the New Method

A graft of the desired thickness and from one-sixth to one-ninth of the raw area to be covered is cut from the donor area. It is placed on stiff sticky paper (I have been using the greasy and sterile paper supplied with boxes of "tulle-gras") or any other material of similar qualities, and skin and paper are cut in strips as thin as convenient (Fig. 1). The strips are again placed on the same type of paper, at the distances desired,

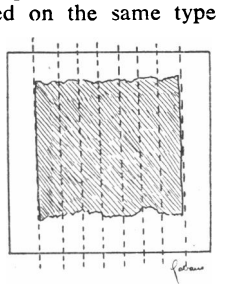

FIG. 1.—The graft, raw side up, is placed on sterile, stiff, sticky paper and cut into strips.

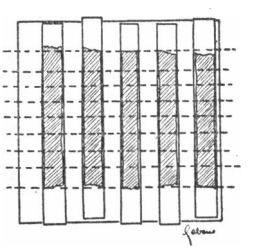

FIG. 2.—The strips, placed on another piece of paper, are cut horizontally.

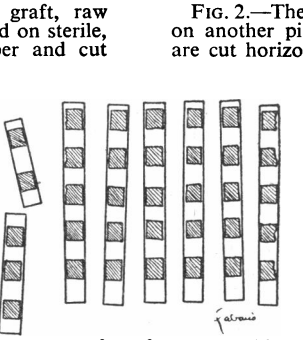

FIG. 3.—Small squares of graft on two thicknesses of paper (only one thickness shown here). The grafts, which retract somewhat, are ready to be placed in position, with the paper.