The very short incubation period would, however, make this improbable unless the infection had been an ante-natal one.

4. The fact that infants seldom or never seem to have a recurrence of the infection after removal to the "septic" nursery has been referred to. On one occasion this did occur, and four infants cured and ready to go out showed a fresh infection simultaneously, two with conjunctivitis and two with a rash on the face. A nurse known to be a carrier of *Staph. aureus* and to suffer occasionally from folliculitis of the nares had been transferred three days previously to this ward. A comparison of her cultures with those of the strains isolated from the infants' lesions showed three of them to be closely similar, and it seems probable that the new infection was derived from her. The table below shows the similarity of the cultures of Nurse A to those from the two cases of conjunctivitis and one pustule.

Cultures from Nurse and Babies of D I Ward

No.	Source	Coagulase	Gelatin	Litmus Milk	Diffusing Subst., up to Dilution of	Haemolysis
1A	Nose (Nurse A)	+	Liquefied	Acid clot	1:10	+
7A	Eye (baby)	+	"	" "	1:10	Slight +
11A	Face pustule (baby)	+	"	" "	1:10	+
12A	Eye (baby)	+	"	" "	Nil	Slight +

Treatment of the Epidemic

Almost inevitably in the first place the organism is derived from a human source and, by-passing the various secondary modes of distribution such as dust, air, and so on, it is at the origin we should deal with it. The infection in its milder aspects might be regarded as not dissimilar to follicular acne in the young adult, and perhaps almost any strain of staphylococcus might cause it; but the severer lesions are almost certainly derived from an active cutaneous infection, most likely a folliculitis. Such a folliculitis occurring in the anterior nares and leading to a damp nose and frequent use of the handkerchief would give rise to rapid dissemination of an organism with increased infectivity. We have so far succeeded in implicating only the one case of this sort described above, from which we think we have definitely traced some infantile infections. It may be that this not very obvious type of lesion is a frequent source of infection, and such infected carriers should be sought for carefully and excluded from the maternity wards. More obvious forms of sepsis are of course excluded as a matter of routine.

Various general measures were carried out, including closing and cleaning of wards, the use of masks by all medical and nursing staff entering the wards, the use of gloves in handling the infants, and the replacement of handkerchiefs by oiled medicated gauze for both staff and mothers. The effect of these measures, if they have had any, is by no means clear. The closure of the wards for cleaning and a few days' airing can certainly be said to have had no value in stopping the infection, which began again in a bullous form within two or three days of reopening. The use of masks for nasal carriers is probably of no value: the removal of both masks and gloves led to no increase in the number of infections. The use of gloves was replaced by dipping the "socially clean" hands in a box of french chalk before handling the uninfected infant, with the object of keeping the hands dry and interposing a barrier of powder between the hand and the infant. The medicated handkerchiefs did not come into use until the epidemic was abating, and it is not possible to say whether they have played a useful part or not. They were prepared as follows: An emulsified oil having properties similar to that suggested by Van den Ende and Thomas (1941) was prepared from the following:

Sulphonated castor oil	..	..	..	50.0	parts
Lanette wax S.X.	..	..	..	5.0	"
Cresantol-3	..	..	..	2.5	"
Paraffin liq. leve	..	..	to	100.0	"

One part of the above was diluted to 5 parts with water before use and tinted with eosin q.s.

Six-yard rolls of absorbent gauze were immersed in the emulsion until saturated and the excess of liquid was removed by wringing; the gauze was then put in a warm place until dry. Portions of gauze about 8 in. square cut to form handkerchiefs were issued twice daily.

In the event of a really serious epidemic which could not be controlled by other methods of hygiene it might be worth while to consider approaching the problem from the other end and attempting to prevent the organism obtaining lodgment in the hair follicles of the infant. This might be possible by occluding them with a natural fatty substance, say a lanolin preparation, containing a sufficient amount of a harmless bacteriostatic substance.

The treatment of carriers with a view to sterilizing the anterior nares is not a very promising field of action so far as permanent cure is concerned. One method, bearing in mind the gradual substitution of yellow by white cocci, would be an implantation of the area with a definitely non-pathogenic staphylococcus—e.g., *Staph. epidermidis albus*. Another possible method might be the use of a suitable bacteriophage.

Summary

An epidemic of bullous impetigo neonatorum due to staphylococcus infection and extending over some months was observed in three maternity wards, and the observations continued for a further 12 months. The outbreak occurred at a period when staphylococcal infections in the district were more frequent and severe than usual. There was, moreover, at this time a considerable increase in the number of cases of acute mastitis. The epidemic was preceded, accompanied, and followed by mild cases of papular impetigo and staphylococcal conjunctivitis. There were no deaths.

Nasal carriers of *Staph. aureus* among the doctors and nurses, infants, and mothers were numerous and continued so after the abatement of the epidemic. It remained uncertain whether the more severe bullous cases were due to an increase of virulence in the endemic infection or to a new infecting agent. It was thought that a folliculitis of the nares was a likely source of infection and that the organism was shaken into the air from the handkerchief. Handkerchiefs were replaced by squares of oiled medicated gauze changed twice daily for all adults in the wards.

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BLOOD TRANSFUSION IN NOCTURNAL HAEMOGLOBINURIA

BY

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Chronic haemolytic anaemia with nocturnal haemoglobinuria (the Marchiafava-Micheli disease, or "nocturnal haemoglobinuria") is an uncommon type of haemolytic anaemia. Its clinical manifestations have been fairly well established, and accounts of about 40 cases are now available. Although the ultimate cause is unknown the mechanism of haemolysis has recently received considerable attention, and the early observations of van den Bergh (1911), Ham (1937), Dacie, Israëls, and Wilkinson (1938), and Jordan (1938) have been followed by comprehensive clinico-pathological and immunological studies by Ham (1939) and Ham and Dingle (1939). Unfortunately, this work has been as yet of little benefit to the patients. There is no specific treatment, and this disorder, although variable in course and severity, ultimately proves fatal. The known haemopoietic substances are useless, and splenectomy is ineffective and dangerous (Hamburger and Bernstein, 1936).

Transfusion has been resorted to on many occasions, and has often resulted in a severe haemolytic episode (Hamburger and Bernstein, 1936; Ham, 1939). Nevertheless, remissions after transfusion have been reported: for instance, a severe reaction in Ham's first case was followed by two weeks' freedom from haemoglobinuria, with only slight nocturnal amounts in the succeeding two weeks; and the same sequence of events followed four more transfusions in this patient. Similar observations were made on his third case. Three transfusions, each of

500 c.cm. of citrated blood, were given on alternate days to his fourth patient, who was in a severe haemolytic crisis at the time. The level of free haemoglobin in the plasma remained extremely high until 24 hours after the third transfusion. The amount of haemoglobinaemia and haemoglobinuria then fell during the next five days to the lowest levels observed in two months' observations, and the erythrocyte count eventually rose from 1,710,000 to 3,550,000 per c.mm.

It seemed possible from these observations that blood transfusion, despite its initial deleterious action, might have a more prolonged inhibitory effect upon haemolysis, perhaps owing to the presence of a naturally occurring antihemolytic substance in the transfused blood (Josephs, 1938). It was hoped that this inhibitory effect, if substantiated, might prove to be a basis for an effective line of treatment, and with this in mind we have administered a substantial amount (2,000 c.cm. over 12 days) of stored (6-weeks-old) filtered human serum to our patient. The object of this paper is to record the results of this experiment and also of an analysis of the effects of a blood transfusion which is as detailed as wartime circumstances allow. The latter experiment was undertaken in collaboration with Dr. P. L. Mollison, who studied the survival of the transfused blood and has kindly allowed us to quote his results.

Clinical History of Case

The patient is a woman aged 38. Her illness dates from Nov., 1940, when she noticed that the urine she passed in the mornings had become dark red in colour. At other periods during the day no abnormality of the urine was noticeable, but there was a slight but gradual deterioration in her general health; lack of energy, fatigability, and breathlessness increased imperceptibly. In April, 1941, her strength was still more impaired, and she was kept in bed at home for five weeks. The onset of pains in her legs along the distribution of the sciatic nerve resulted in her admission into another hospital, where she received treatment for sciatica. Anaemia was recognized and iron was given as treatment, but the significance of the intermittent dark urine was not appreciated and no diagnosis was made. There was some improvement as the result of rest in bed, and she restarted clerical work in Oct., 1941. She kept at work until June, 1942, when jaundice of moderate intensity and increasing weakness forced her to rest. The abnormal discoloration of the urine passed in the early morning had been a characteristic feature of her illness and had been rarely absent since the onset.

She was admitted into Leatherhead Emergency Hospital on July 1, 1942. She was seen to be a well-nourished woman of medium height and 8 st. 12 lb. in weight. There were no unusual physical stigmata except an easily perceptible jaundice of her sclerae and a curious combination of pallor, jaundice, and a slight brownish pigmentation of skin and mucous membranes. The tint, which is striking, appears to be a characteristic of the disease. Physical examination revealed no abnormalities except that the tip of the spleen was just palpable. The liver was not felt and the superficial lymph nodes showed no gross enlargement. X-ray examination of the kidneys did not reveal any deposits of haemosiderin.

Inspection of samples of urine showed the presence of haemoglobin at certain times of the day, characteristically in the samples passed between the early hours of the morning and 9 a.m. The urine was usually quite free at other times. The amount of blood pigment present varied; there was often enough to produce a deep port-wine discoloration.

Laboratory Investigations

Blood count on admission: erythrocytes, 2,180,000 per c.mm.; haemoglobin, 46%; C.I., 1.06; cell volume, 24.5%; m.c.v., 113 μ^3 ;

reticulocytes, 10%; total leucocytes, 5,500 per c.mm.—polymorphs 59%, myelocytes 0.5%, metamyelocytes 3%, lymphocytes 36%, monocytes 1%, eosinophils 0.5%. Van den Bergh test, prompt reaction negative; total bilirubin, 1.4 mg. per 100 c.cm. Blood group A. Gastric residuum, achlorhydria with a moderate secretion of free acid after an alcohol meal. Bone-marrow biopsy (sternal puncture) showed active erythroblastic hyperplasia, the nucleated erythrocyte-leucocyte ratio being 1:2. Primary erythroblasts of all states of maturity were present, early types being relatively uncommon and haemocytoblasts still less frequent (less than 5% of total nucleated erythrocytes); normoblasts were also scarce, and there was no premature ripening of the cytoplasm of the primary erythroblasts. The leucocytes showed no noteworthy change.

Serological tests confirmed the tentative clinical diagnosis. It was demonstrated: (i) that a proportion of the patient's cells were lysed *in vitro* after 1 hour's incubation at 37° C. in autogenous fresh serum or that of normal subjects of the same group; (ii) that lysis was sensitive to changes in pH, and was increased by the addition of fresh guinea-pig serum from which all anti-human heterolysin had been absorbed; (iii) that the patient's cells were not lysed by guinea-pig serum in the absence of human serum; and (iv) that normal cells were not lysed by the patient's serum under any conditions. These observations are characteristic of nocturnal haemoglobinuria, and for this reason will not be elaborated further in this paper.

Transfusion of Stored Serum

After three weeks' observation 400 c.cm. of six-weeks-old filtered human serum was given intravenously in 90 minutes on the morning of Aug. 20. The patient felt none the worse, but the urine specimens during the afternoon contained much free haemoglobin. A specimen

passed at 11.45 p.m. was, however, free from pigment, as were all specimens passed the following day. The regular nocturnal rhythm restarted, however, on the morning of Aug. 22, and persisted until the 25th, when a further bottle of serum was given. The immediate onset of gross haemoglobinaemia and haemoglobinuria was again followed by a period of freedom, only interrupted when further bottles of serum were given on Aug. 27 and 29 and Sept. 1. The urine remained clear until Sept. 10, except for a trace of pigment on Sept. 6. This remission was longer than any the patient could remember since the beginning of her

illness, but unfortunately any such improvement was not reflected in laboratory investigations. The haemoglobin was observed to have risen by only 2% and the erythrocytes from 2,170,000 to 2,370,000 per c.mm., changes which are not significant. Moreover, a standard *in vitro* test* showed no alteration in the sensitivity of the patient's cells to haemolysis by her own serum.

The constant occurrence of marked haemoglobinaemia and haemoglobinuria after the administration of serum was unexpected. The complement content of the serum transfused was estimated against sensitized sheep cells to be less than 1/32 of that of the patient's own fresh serum, and its content of anti-A agglutinins negligible (the patient's cells were not agglutinated *in vitro* at a serum dilution of 1:2). Moreover, the transfused serum had no haemolytic activity *in vitro* on the patient's own cells in the absence of fresh serum. The reaction of the serum, which had been estimated to be slightly more acid than that of blood, was on the last two transfusions deliberately made more alkaline (pH 7.9) by bubbling oxygen through the serum for 10 minutes before administration. Haemolysis was not inhibited by this procedure, and it was tentatively concluded that lysis was most likely caused by the presence

* *In Vitro Test*.—0.1 c.cm. of a 6% suspension of washed patient's erythrocytes in 0.9% NaCl was added to 0.5 c.cm. of acidified patient's serum (serum 0.3 c.cm., N/20 HCl in 0.9% NaCl 0.15 c.cm., 0.9% NaCl 0.05 c.cm.; pH approximately 7.2). The amount of haemolysis produced by one hour's incubation at 37° C. was estimated visually against standards.

The effect of serum and blood transfusions on a patient with nocturnal haemoglobinuria.

within the transfused serum of relatively stable components of complement (not lytic by themselves) in sufficient concentration to increase the haemolytic power of the patient's own serum.

Transfusion of Whole Blood

On the morning of Sept. 11, after the administration during the previous day and night of enough alkali to make the urine alkaline, the patient was given 500 c.cm. of a concentrated cell suspension of Group O citrate-glucose blood within 90 minutes. Before the transfusion had been quite completed symptoms suggestive of a haemolytic episode began to make their presence felt. The patient complained of a slight dizziness and backache, and a little later felt sick. These symptoms slowly progressed but never became really severe, although there was some diarrhoea and sickness during the following night. Her temperature was slightly raised, the maximum being 100.2° F. Within 24 hours of the transfusion the feeling of sickness abated and it seemed clear that the constitutional symptoms were subsiding. The patient had, however, by then become strikingly brownish-yellow in colour; the brownish tinge disappeared within a few days, but the jaundice persisted longer. Soon after the termination of the transfusion intense black urine was passed, and it continued in this state for the next 48 hours; but by the morning of Sept. 14 only a small amount of pigment was present, and the specimens passed on the 15th were clear. The urine then remained clear until Oct. 30.

The effect upon her blood is illustrated in the accompanying chart. This records (a) the total erythrocyte level, (b) the number of donor cells present, and (c) the level of the patient's own cells after the transfusion (a less b). The haemoglobin and reticulocyte percentages are also recorded and the presence or absence of haemoglobinuria and the results of the *in vitro* haemolysis test indicated. Study of the chart reveals several points of interest. The number of normal (donor) cells present after transfusion agreed well with expectations, there being a little more than 1 million per c.mm. This figure slowly and gradually fell, and approximately 18% of the transfused cells were still surviving 95 days after transfusion. This is essentially a normal rate of elimination (Mollison and Young, 1942). Despite the presence of 1 million per c.mm. or more of normal cells the total erythrocyte count had fallen slightly at the end of 24 hours, indicating great destruction of the patient's own cells—i.e., a fall from 2,370,000 to 1,060,000 per c.mm. The count remained at about the level of 1 million per c.mm. for 10 days or so and then rose fairly steadily, just reaching 2,500,000 per c.mm. in six weeks. The total erythrocyte count, after falling about 300,000 per c.mm., reached its pre-transfusion level in 14 days and then steadily rose to 3,180,000 per c.mm. four weeks later. The total count then slowly fell back to its pre-transfusion level of about 2,250,000 per c.mm. The reticulocyte percentage followed the erythrocyte count in an inverse manner.

The percentage lysis observed in the standard *in vitro* tests was not significantly altered by the serum transfusions; after the blood transfusion there was a period of at least a week in which the sensitivity of the cells to lysis *in vitro* was clearly diminished even after making allowance for the presence of many normal cells. This may be due to the removal from the circulation of the most sensitive cells during the haemolytic crisis precipitated by the transfusion. It is interesting to note that sensitivity to the *in vitro* tests had been fully restored, and even appeared to be slightly increased, before the onset of haemoglobinuria, and that the latter did not reappear until the erythrocyte count had regained its pre-transfusion level. No doubt the presence of haemoglobinuria depends upon the renal threshold and the amount of haemoglobin liberated into the circulation per unit time, and is therefore more likely to be found at high rather than low levels of erythrocyte counts if the proportion of cells destroyed is a constant one.

Discussion

It is generally agreed that the basis of this strange disease is an undefined abnormality of the patient's erythrocytes which causes them to haemolyse in the presence of human serum both *in vivo* and *in vitro* (see Ham and Dingle, 1939). Our observations are consistent with this hypothesis and do not support any alternative theory; in particular the possibility that the patient's erythrocytes were sensitized by the presence of an immune body or other haemolytic agent would appear to be negated by the unimpaired survival of the transfused normal cells, unless it were assumed (without any evidence) that the hypothetical haemolytic agent was strictly autospesific.

Similarly, no evidence was forthcoming in support of the further possibility that lack of an antihaemolytic factor was responsible for the excessive breakdown of the patient's cells. Serum transfusions were without significant effect, and the ultimate rise in blood count following the blood transfusion appeared to be due to the good survival of the transfused cells. The patient's own cells did not increase significantly in numbers.

Summary

A short clinical description is given of a case of chronic haemolytic anaemia with nocturnal haemoglobinuria (Marchiafava-Micheli disease).

Two litres of stored normal serum was given intravenously within 12 days; no appreciable effect on, *in vivo* or *in vitro* haemolysis resulted.

A blood transfusion was followed by a severe haemolytic episode in which rather more than one-half of the patient's own erythrocytes were destroyed. The survival of the transfused blood was, however, unimpaired. The transfusion was followed by a remission from haemoglobinuria lasting 6 weeks.

The bearing of these observations on the pathogenesis of the disease is briefly discussed.

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TREATMENT OF PSYCHIATRIC PATIENTS IN GENERAL HOSPITALS

A SOCIAL EXPERIMENT

BY

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For centuries the peculiar symptoms of nervous and mental disorder have caused segregation to remain paramount over other aspects of treatment. This policy has been accepted, though with suspicion, by the main body of public opinion, but strongly resisted by individual patients and relatives. In Britain several thousands of patients are annually permitted to become chronic cases before specialized treatment is sought in a hospital for mental or nervous disorders because so many people, with or without good education, still regard these illnesses either as irrecoverable or to be treated conservatively at home as long as possible. Many a patient suffering from early psychosis could have avoided prolongation of illness, subsequent certification, and economic loss if either he or his relatives had not had the mistaken conception that on admission to hospital there was risk of being made worse by association with chronic patients, that active treatment scarcely existed, or that he would never be discharged. These ideas have their roots in the past, when the chief form of treatment known was to minister to the well-being of the patient on general lines as efficiently as overcrowding would allow. Under these conditions the better the quality of the personality the more likely was the individual to defer accepting hospital care, except in the most acute disorders.

Some idea of the cost of this policy may be gained from the estimation (Ebaugh, 1940) that, in the U.S.A., hospital beds are required for 100,000 patients becoming chronic annually, and in 1940 chronic psychiatric patients occupied half the total number of hospital beds. Many more are maintained in their own homes or in private nursing homes. The problem is little different in this country; for example, the London County Council in accommodating their own share of the burden require, out of a total of 72,000 beds for all types of illness, 34,000 for psychiatric patients, a large majority of the beds being for chronic cases. Another aspect is shown by Sargent and Cook (1942), who reported that 20% of the cases admitted to the medical wards of a general hospital were found to present conditions and problems primarily neuropsychiatric, regardless of the patient's initial complaint or the preliminary diagnostic impression. Heldt (1940) also places the percentage at 20 or 30, and remarks that if mention be made as well