INVESTIGATIONS DURING AN OUTBREAK OF BULLOUS IMPETIGO NEONATORUM

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Outbreaks of impetigo neonatorum apparently due to staphylococcal infection were undoubtedly much more frequent than usual during the autumn and winter of 1941, more especially in maternity hospitals and homes. It is possible that staphylococcal infections in general were increased, as is shown in the following comparative figures of in-patients operated on in a large general hospital in London.

	Oct., 1940, to March, 1941	Oct., 1941, to March, 1942
Carbuncle	6	15
Mammary abscess	11	19

The outbreak affected three maternity wards, and the main inquiry covers the four months Nov., 1941, to Feb., 1942. The three wards are on different floors of the same block, each with its own nursery, labour ward, accommodation, and staff complete. The nursing staff mix in a general way when off duty, and more closely at lectures twice weekly. Cases affected during this period number 162, though this figure includes many very mild cases. There were no deaths.

Course of the Epidemic

For many years there have been occasional cases of staphylococcal conjunctivitis in the maternity wards and rarer isolated cases of mild impetigo. In October cases of impetigo increased, and in November there was an acute outbreak. The case rate was highest during November and December, and the severity of the condition at this time was marked clinically by many cases showing large areas of small bullae which rapidly suppurated and which were associated with a papulo-pustular rash. Occasional cases of conjunctivitis continued to occur, but they showed no obvious increase of severity. After December the case rate fell, with occasional increases, and the type became as a rule much milder, consisting of a scattered papulo-pustular rash, often of only a few red spots, though a few bullous cases still occurred.

During the following 12 months the record of infections was continued, and it was found that after the disappearance of the bullous cases the mild papular type of infection continued to occur in considerable numbers, ranging from 5 to 15% of all infants; the condition might in fact be described as endemic. In the records of the epidemic period no attempt had been made to differentiate between the papular and the bullous infection, all being sent to the septic ward as cases of impetigo of varying degrees of severity, although previous to this time mild impetigos and conjunctivitis cases had not been segregated. In the light of these later observations it seems possible that the bullous type was an entirely new epidemic infection superimposed on the endemic condition.

Particulars of the Outbreak

Clinical Appearances.—The general health did not seem to be affected in the least. In both severe and mild types the rash appeared suddenly, though in a few cases a preliminary erythema had been reported; then red papules, and clear blisters which rapidly became opaque and suppurated. In severer cases

the bullae were close-packed. Sometimes strikingly bilateral groups on the cheeks, neck, or inner sides of the thighs were seen. The bullous lesions were very superficial; they dried up, exfoliated, and left a smooth epithelial surface. No scarring resulted. Almost the whole of the rash "came out" at once, and there was very seldom any continuation of the process after the first two or three days, though during that time spots might continue to come out under the gentian violet paint. Recurrence while the baby remained in the "septic" nursery was not seen, though an exception to this will be referred to later. In the case of the bullae the actual site of infection was not clear, but the papular type of rash appeared to be a follicular infection; only one case was seen in which the palmar surface of the hands was affected. There were no deaths and no opportunity for a biopsy. At the height of the epidemic the bulk of the lesions were of bullous type; as the case rate fell the lesions became almost entirely papular and much more sparse, many cases having only an occasional papule.

Site of Lesions.—An analysis of 40 cases showed the favourite sites of the lesions to be: face and neck, 14; conjunctivae, 8; abdomen, 5; scalp, 4; thighs (inner sides), 4. Chest and back were rarely affected, and eyelids, nose, ears, feet, and hands not at all. Several cases affecting the eyelids (blepharitis), one in the temporal region, one on the palmar surface of the hands, and several on the margins of the axilla have since been noted. In spite of the fact that practically all of these infants were carriers of *Staph. aureus* in the nares, no instance of real infection of this area or the adjacent upper lip was seen.

The **incubation period**, or rather the average age at onset, was 9 days (estimated from a series of 30 cases). The oldest patient was 22 days, and the youngest in which a real infection was seen was 2 days. Many cases, of course, were discharged about the 10th to 14th day, and may have developed a rash later, though inquiries in the casualty department did not suggest this.

Infection by Direct Contact.—Skin infection of the mothers either before or after onset in the baby was not noted, at any rate not with a similar type of lesion. There was one exception. The mother of an infected child had a breast abscess (subsequently bilateral). Within a day or two after incision a sharp belt of small superficial purulent bullae appeared below the breast from the axillary fold to the midline. The condition did not suggest herpes, and it cleared up quickly. The other breast was subsequently opened and drained, but, except for a single spot, the rash did not recur. A vertical band of skin below the breast had been painted prophylactically with gentian violet; the spot occurred in the middle of this. Of the **nursing staff** who handled the infected babies one sister early in the epidemic developed a perionychia. She left hospital before it was opened. It was presumably a staphylococcal infection, though not necessarily derived from her charges. Contact infection of nurses in the maternity or septic nursery was not observed. Among **infants** the direct infection of a healthy child from an infected one would appear to be an unusual event even given the most

favourable circumstances. The infected infants were isolated in a "septic" nursery, and their mothers were removed to the adjacent ward. Into this ward were also taken mothers who themselves had infective lesions, such as mammary abscess, and when this happened their infants, though quite healthy, went into the septic nursery. In five instances during the epidemic healthy infants were kept in this nursery mostly for several weeks. None of these infants developed an impetigo, although one of them had a single papule which rapidly cleared up. The nurses did not wash between cases, and each infant took its turn for changing with the rest on the same ward table. The infective agent must have been easily available, and we can only suppose that its infectivity was not high or that the appropriate susceptibility was not present in these five cases. In one instance pus containing an abundance of staphylococci was taken from a fresh lesion of the trunk and painted on an area of clean skin two inches below the infected patch; no infection resulted.

The Infective Agent.—In the early severe bullous types of infection a streptococcus was suspected, but this organism was not found in careful culture on specific media. Diplococci were present scantily in films from the clear fluid of the early bullae: later, frank pus and staphylococci were seen. In cultures, whether from infected eyes, bullae, or pustules, the only organism obtained was the *Staph. aureus*, and we have assumed this to be the infective agent. (In a few of the later mild papular cases a white staphylococcus was grown.) An organism with the morphological and cultural characters of *Staph. aureus* can be obtained from many sources, and though many harmless varieties or strains may be presumed to exist there is at present no certain way of identifying a pathogenic strain apart from isolating it from a lesion.

Virulence and Infectivity.—It is a well-established fact in both experimental and epidemiological research that an organism passed from case to case increases for a time in pathogenicity and in infectivity corresponding with an increase in the case rate and the severity of the disease. An epidemic fades out in part by a loss of these characters in the infective agent, partly by a development of immunity in the population (many of whom may become carriers), and partly for lack of suitable material to infect. In this epidemic or outbreak the case rate and virulence (judged by appearances, for there was no mortality) were certainly high at the same time and declined together. We know that the epidemic did not abate for lack of suitable pabulum, since this was renewed daily in the form of newborn babies. We might attribute an increased case rate alone to some sudden access of infected fomites such as insanitary laundering, but where the severity rises and then falls with the case rate on a constant basis of infectable population we must assume some change in the attributes of the infecting organism, probably by passage. This does not necessarily mean that the infants were infected directly from each other—there is, as already shown, little evidence in support of such a direct transfer. Although the simple carrying of an organism on a moist mucous membrane is not likely to exalt its virulence, it is possible that this change was taking place as a result of actual infection, probably in the nares of a carrier or carriers. Since three separate wards were affected at once we should have to assume at least one basic source of infection and a number of other persons carrying the virulent organism.

Another explanation of the apparent exaltation of virulence, as pointed out earlier here, is that an entirely new infection was superimposed and led to the bullous lesions. In favour of this view is the fact that the bullous cases seemed to occur quite suddenly, although they faded out more slowly and with a decreasing severity.

An attempt was made during the epidemic to differentiate between the infecting agent of the bullous and the papular types, but by such means as we used no characteristic difference was found. Serological typing was not available.

Where the Organism is Harboured

Nasal Carriers.—In the anterior inch of the nares where the skin is squamous, moist, and slightly alkaline, a carrier condition is apt to develop. In our series, judging from a few cases in which additional cultures were taken from inside the nasal

passages with a speculum, the organisms were limited to the anterior part. Carriers of *Staph. aureus* in this position were common among the doctors and maternity nurses; as many as 85% of the latter were carriers at one time. The carrier rate among the nursing staff was followed at approximately fortnightly intervals for some 6 months. It was a somewhat uncertain procedure, depending on the development of a golden colour in the colonies after 24 hours in the incubator and a further 24 hours on the bench. As every infection cultured at this time produced a bright golden colony we accepted this as the criterion. The correlation between the case rate and the carrier rate was not a very close one. The latter reached its highest point (85%) towards the end of the most severe part of the outbreak—i.e., the beginning of January—but it was still at 70% at the end of February, when the severe bullous cases had practically ceased; it stood at 50% in April, and was down to 25% in June.

Several heavy carriers of *Staph. aureus* were present in each of the wards throughout the whole period of observation. It seems probable that this wholesale carrier state was related to deficient ventilation during the long periods of black-out. The strains isolated from carriers were in all cases coagulase-positive, and though it is not to be supposed that all were capable of causing infection it is reasonable to suppose that some were. During April and May, when the numbers were declining, some *Staph. aureus* carriers began to show colonies of *Staph. albus*; these were coagulase-negative, while the associated *Staph. aureus* remained positive.

During the winter months the carrier condition was obviously widespread; about 30% of the women admitted for labour, and nearly 100% of babies 10 days old in our nurseries, were carriers. A children's ward at the other end of the hospital showed at this time that 50% of the nurses were carriers, as were 30% of the children under 5 years.

The presence of cocci in very large numbers in the nares of a carrier is not usually associated with any obvious sign of inflammation; but a few cases of sore nares with folliculitis are found, and it is possible that these are the originators of the infection. The organisms carried are in most cases presumably derived from the air; they must, however, have a special affinity for such a locus, since cultures from the air of the wards showed that various forms of *Staph. albus* and pale staphylococci were the predominant organisms, and that *Staph. aureus* is relatively rare even in rooms inhabited by carrier nurses and infected babies. *Staph. aureus* may also be present in the throat, though much more rarely than in the nose (in our series 5 to 15%); from these latter cases droplet infection might of course take place. Cultures from the nasopharynx were not carried out.

Dissemination.—Droplet-spread from the nose must be rare: even in sneezing almost all the droplets come through the mouth. Tests taken by shaking the used but apparently clean and dry handkerchief of a carrier over a culture plate, however, showed the dissemination of hundreds of viable organisms similar to those present in the carrier's nares, and it seems more than probable that it is mainly in this way that the bacteria get into the air and spread from one person to another. Yet cultures from the air of the wards during the epidemic did not show *Staph. aureus* in large numbers. On 3-in. culture plates exposed for half an hour during bed-making, among hundreds of colonies—mostly skin saprophytes such as *Staph. albus*, skin diphtheroids, and sarcinae—six colonies of *Staph. aureus* were the maximum found. Again, on fomites such as door-handles, light switches, and so on, a real *Staph. aureus* was hardly ever found, though paler yellow varieties and *Staph. albus* occurred.

On the other hand, finger-prints after handling a carrier's handkerchief showed a considerable number of the infecting organisms. When gloves were worn and the handkerchief was handled, organisms in the finger-prints were far fewer, and when the gloves had been lightly powdered with french chalk the growth derived from handling the handkerchief was practically negligible. Ward dust as such was not investigated. A good deal of work has been done on this subject by various people, and if the bacteria are present in the air it may be taken for granted that the floors, window-ledges, and black-out blinds have not escaped. Quite early in the epidemic *Staph.*

aureus was found in small numbers in the ward soap used for washing the babies, and from then on soap was completely interdicted and the infants rubbed with oil of arachis.

Implantation of Infection

The Skin of the Newborn.—The skin of the newborn does not show very marked differences from that of the adult. In a section from the neck the patulous funnel-shaped hair follicles appear to be wider than those of the adult in the same area and more closely crowded. There are fewer layers of epithelium, and at the base of the funnel, where the sebaceous glands open, the epithelium in infants may consist of only one layer of flattened cells. The sweat-gland orifices also show in the infant's skin as definite pits leading down to the sweat ducts, and may equally well be the seat of infection. In the one case of purulent bullae observed on the hands no doubt infection did take place by this route. These are definitely weak spots in the body covering, as well as ones likely from their shape to harbour infective organisms. It might well be that the implantation of bacteria of quite low infectivity and virulence in such sites would set up an infection.

Time of Implantation.—An investigation was carried out to try to discover the time of implantation of the infection.

1. Swabbings were taken from the vagina and thighs of ten mothers—*Staph. aureus* was not obtained from any of these. Implantation from the vagina may be regarded as rare, though it probably does occur, and two cases are described below.

2. Swabbings were made from the skin of the babies in the nursery, on the cheeks and inner parts of the thighs. Only 5 babies were tested—on the first, third, and sixth days after birth. Cultures were also made from the nares on each occasion. *Staph. aureus* was present in the nares in two cases on the first day and in four out of the five in great abundance by the sixth day. This organism was found on the cheeks in small numbers in three cases on the first day, one case on the third day, and three cases on the sixth day. On the thighs it was found only once, and that on the third day; none of these cases was or became infected up to the time of discharge. These figures are small, but they show that *Staph. aureus* may be present, on and off, on the skin of a healthy baby almost as soon as it is put into the nursery. They also show a great preponderance of implantation on the exposed areas; and that the presence of a staphylococcus on the skin does not necessarily lead to infection. Staphylococci on the cheeks may of course well come from the infant's own nose, which harbours them from an early date, and such a strain might or might not be pathogenic; but it is a striking fact that an actual infection of the nares or adjacent upper lip has not so far been encountered.

3. An obvious point of contact for the baby's face is the mother's breast and probably hands.

In an investigation to show whether the infant was likely to be infected from the mother's milk 9 cases were examined. Cultures were made from the milk on the first, third, and sixth days of the puerperium. The milk was expressed into a tube by the nurse, after cleaning the nipple, before suckling began. The milk contained *Staph. aureus* in five cases on the first day and a further two by the sixth day. In only two was the milk found uninfected on the sixth day. One of these nine infants later developed impetigo, but it belonged to a mother whose milk had remained negative throughout the investigation. These figures again are scanty, but they tend to show that the presence of *Staph. aureus* in the milk does not usually lead to infection of the baby; nor, of course, does the presence of these organisms usually lead to an infection of the breast. Even when the mother has developed an acute mastitis, thereby showing the presence of a pathogenic strain of cocci, the infant is most unlikely to contract an impetigo, though perhaps as a rule by that time it is past the usual age for infection.

Factors aiding Infection

Abrasion.—Babies are laid usually on one side or the other, and it is likely that movement of the head on rough woollen fabrics may cause irritation. There is no proof of this beyond the fact that the sides of the face were most frequently the sites of infection. We have already seen that they are a common site of implantation, and the turning of the child might lead to the common bilateral infection. On the other hand, a child had a forceps bruise on the cheek, breaking the skin in two long lines. It later developed a severe blister rash all round the neck and occipital regions; the area with the broken

skin did not become infected, though the opportunities for implantation of bacteria must have been legion. This suggests an affinity of the infecting agent for epithelial rather than the deeper dermic tissues. We see the same point in the shallow bullous lesions and absence of scarring.

Heat, Moisture, and Alkalis.—The napkin area, especially the inner sides of the thighs, while not a very common site of infection, is subject to heat, moisture, and alkalinity. This region is apt to show circumscribed areas of closely massed papules or bullae, sometimes bilateral, suggesting perhaps special facilities for a rapid local spread of infection from a small unnoticed papule. Excessive warmth alone does not seem to favour infection. Thus three premature babies were kept at high temperatures with hot bottles in a nursery in which infected cases occurred from time to time. Only one of these developed a single papule at the end of the third week. This would be about the ordinary incidence of infection at that time. The destructive effects of alkalis on the amino-acids of the squamous epithelium is well known, and ammonia quickly develops in a wet napkin. Such lesions as occur in the napkin area are usually on the inner side of the thighs and pubic region; they were not seen actually on the genitalia. The question has also been raised whether the alkalinity of soap did not weaken the epithelium and lead to infection, but in the cases here reviewed soap had never been used.

Identification of Types or Strains of Staphylococci

In this research we might have two aims: (1) To identify a particular organism in whatever circumstances we may find it—for instance, to trace a carrier's strain in the lesions of an infected case. In one instance we believe we have been able to do this. (2) To identify a staphylococcus as pathogenic by some other criterion than taking it from an infection. The problem lies in the similarity of strains of *Staph. aureus* from the most varied sources in their reactions with the usual biochemical tests. Some 40 cultures, including those from air, nasal carriers, impetigo lesions, and known staphylococcal infections from other sources, were compared. The tests used were coagulase, haemolysis, and the hyaluronidase (diffusion factor) reaction (McClean). Of the cultures 39 were coagulase-positive. In the case of the other tests the results were very variable.

It could be said that in our hands none of these tests bore any definite relation to proved pathogenicity in any particular culture. They were used here only with the object of correlating and identifying strains from different sources. Serological typing was not available, but even if it had been it does not follow that the antigenic structure of an organism of this sort would be a guide to its infectivity.

Some Unusual Cases

1. An infant 14 days old developed small purulent blisters in a line across the front of the proximal phalanges of both hands and on the adjacent palm and inner aspect of the thumbs. These contained a very pale staphylococcus. They were probably due to direct contact with the mother's breast or fingers. This was not confirmed.

2. Two cases became infected on the second day and showed very similar lesions. The rash was of a fine papulo-pustular type with a red base, and was spread diffusely, mainly on back and shoulders. Cultures grew a nearly white staphylococcus. In both cases vaginal swabbings from the mother produced a similarly pale staphylococcus. The maternal and infant strains in both cases were similar in appearance, and all four were coagulase-positive. No further investigations were made. It seems probable that both of these cases were vaginal infections, especially bearing in mind that these infants had not been washed since birth. Both cases cleared up entirely in a few days. One of the mothers had an unexplained puerperal pyrexia.

3. An infant developed on the third day a closely packed rash of small clear blisters limited to, and more or less covering, the area supplied by the posterior roots of the second, third, and fourth cervical nerves—that is to say, the occipital and temporal regions, including the auricles, the neck, and the upper part of chest and shoulders. Later one eyelid developed a fringe of small styes and some spots on the same cheek. The face and main part of the scalp were unaffected. Cytological examination of the blister contents in the early stage showed the presence of 75% lymphocytes and 25% polymorphonuclear leucocytes. Cocci were present in the early stages and *Staph. aureus* grew scantily. Later the bullae became frankly purulent. Scrapings of the epithelium from inside the bullae in the early stages were examined for inclusion bodies, but without success. It was thought from the disposition and cytology that a neurotropic virus might have been concerned in this case.

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

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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