PEMPHIGUS NEONATORUM CAUSED BY STAPHYLOCOCCUS AUREUS TYPE 71

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Recent work has shown that most of the staphylococci isolated from the lesions of impetigo contagiosa are of a type uncommon in other situations, and are defined by their susceptibility to the typing phage 71 (Spittlehouse, 1955; Parker *et al.*, 1955; Barrow, 1955).

In this paper we describe a small epidemic of pemphigus neonatorum caused by staphylococci of the same phage-pattern. The outbreak took place during the course of a general investigation of staphylococcal cross-infection in the nursery wards of a maternity hospital. During the outbreak, and for four months before it, cultures for staphylococci were made from all cases of neonatal skin sepsis and from various other sources described below. As a result it was possible to trace the staphylococcus subsequently responsible for the pemphigus from its introduction by a nasal carrier and during its dissemination in the hospital.

All the staphylococci referred to in this paper were coagulase-positive.

Bacteriological Methods.—Swabs were moistened with saline before use. Settle-plates were exposed for two hours. Cultures from blankets and garments were made by the sweep-plate technique (Williams, quoted by Blowers and Wallace, 1955). Coagulase-positive staphylococci were isolated and investigated as described elsewhere (Alder *et al.*, 1955), except that the phages 71 and 80 were added to the set of typing phages (Williams and Rippon, 1952), making 21 in all.

General Investigation of Staphylococcal Cross-infection

There was one nursery on each of the three floors of the hospital, that on the first floor being occupied by premature infants. The investigation was carried out on the second and third floors, which on the average contained 25 and 18 cots respectively.

The study began on September 18, 1955—that is, 18 weeks before the first case of pemphigus. This study is still being carried on, but only the results obtained in the period up to February 3, 1956, are given in detail, because the outbreak came to an end then. During the 20 weeks, 385 babies were accommodated in the two nurseries. The noses of 227 of the babies were swabbed repeatedly until they yielded *Staph. aureus*. By the fourth day 67.1% were positive. Swabs taken from normal skin on the back of the neck, the umbilical region, and the groin often yielded *Staph. aureus*; 75% of those from the umbilical region were positive on the second day of life.

Nasal and hand swabs were taken once a week from the nurses on day duty in the nurseries, except for those who happened to be off duty at the time of swabbing. Also,

staphylococci isolated from the noses and hands of nurses before joining the hospital were kindly sent to us from the Department of Preventive Medicine, University of Bristol. Nasal swabs were taken from 85 mothers on admission to the hospital. Two settle-plates were exposed three times a week in each nursery. From November 15 cultures were taken from the babies' garments and bedclothes. The practice of the hospital was to send all articles to the laundry as soon as they were used. Babies' garments and bedclothes from both floors were washed together (the woollens at a lower temperature than the non-woollen goods), but were kept separate from other laundry. Cultures were made from 144 cot blankets, 62 woollen vests and jackets, and several cotton articles. All of these had been freshly laundered except for a few of the blankets. Many of the woollens yielded heavy growths of bacteria, which often included staphylococci. The non-woollen articles, which had been more strongly heated, yielded very scanty growths and no staphylococci.

From all these sources 874 coagulase-positive staphylococci were isolated, 551 of them being penicillin-resistant. In addition, 13 pustular lesions of babies' skins and 17 cases of neonatal conjunctivitis yielded coagulase-positive staphylococci. The staphylococcal cross-infection on the two floors was about equal in amount, as judged by bacteriological and clinical observations. The clinical infections were mild, and were very few in comparison with the numbers of staphylococci which were isolated. Except for the cases of pemphigus described below, they consisted entirely of conjunctivitis and of skin pustules, which were usually small and trivial.

We hope to report in a later paper our observations on the staphylococcal cross-infection as a whole.

Cases of Pemphigus

There were nine cases, none of which was seriously affected (Table I). The first was a baby on floor 3 who developed the disease on January 23, 1956. There were

TABLE I.—Cases of Pemphigus Neonatorum

Case	Date of Onset	Day of Life	Floor	Site of Bullae	Phage-types of Staphylococci
1	23/1/56	10	3	Scalp, finger, eyelid, chin	<i>Staph. aureus</i> type 71
2	24/1/56	7	3	Fingers, cheek, chin	" " " 71
3	24/1/56	10	3	Umbilicus, leg	" " " type
4	25/1/56	9	3	3 fingers	<i>Staph. aureus</i> type 71
5	25/1/56	8	3	Thigh	Not cultured
6	27/1/56	8	2	Fingers and forearm	<i>Staph. aureus</i> type 71
7	30/1/56	12	3	Umbilicus	" " " 52A*
8	3/2/56	7	3	"	" " " type
9	3/2/56	6	3	"	" 6/7/54/70+* Not cultured

* See text for possible explanation of failure to isolate *Staph. aureus* type 71 from these cases.

seven more cases on floor 3, and one on floor 2. The latter (Case 6) had been delivered by caesarean section in the operating theatre on floor 3, and his first garments had been provided by the nursery on that floor.

Swabs from the bullae of seven of the cases were cultured, and all gave profuse growths of *Staph. aureus*. Four of them, including the first two cases, yielded penicillin-resistant staphylococci lysed by phage 71 but by no other dilute phage. They were lysed by other group II phages at 1,000 × R.T.D., and thus were the same as the "normal 71" strains of Parker *et al.* (1955). From three others, type 71 staphylococci were not isolated. These negative results may have been due to failure to examine the cultures thoroughly enough. By mistake, the plates were discarded after one colony from each plate had been picked for typing. All three cultures from which we failed to isolate type 71 staphylococci were from already ruptured bullae near the umbilicus. Staphylococci of various phage patterns were

often present in large numbers on normal skin in this area, and cultures of ruptured bullae would no doubt often contain more than one strain.

Staphylococci of type 71 had not been identified previously in the hospital. However, a number of the cultures which had been isolated from various sources since late November, 1955, had not then been typed. Completion of this work revealed that one nurse, Nurse C, who joined the staff on November 30, 1955, was a persistent heavy nasal carrier of type 71 penicillin-resistant staphylococci, and that similar staphylococci had been isolated subsequently from a variety of sources, chiefly on floor 3 (Table II). All these strains

TABLE II.—*Sources and Dates of Isolation of Penicillin-resistant Staph. aureus, Phage-type 71*

Date	Floor	Site
30/11/55	3	Nurse C's nose
14/12/55	2	Settle-plate
6/1/56	3	Nurse C's nose
6/1/56	3	" " hands
13/1/56	3	" " nose
17/1/56	3	Used blanket
17/1/56	3	Freshly laundered vest
17/1/56	3	A baby's normal skin, near umbilicus
18/1/56	3	Settle-plate
19/1/56	3	A baby's normal skin (groin)
20/1/56	3	Two freshly laundered woollen garments
20/1/56	3	Settle-plate
20/1/56	2	A nurse's hand
23/1/56	3	A baby's normal skin (neck)
23/1/56	3	Pemphigus lesions of scalp, finger and chin (Case 1)
23/1/56	3	Two settle-plates
24/1/56	3	Pemphigus lesions of finger and chin (Case 2)
24/1/56	3	Freshly laundered woollen garment
26/1/56	3	Pemphigus lesions on finger (Case 4)
27/1/56	2	Pemphigus lesions, fingers and forearm (Case 6)
27/1/56	2	Used blanket

were resistant to penicillin but sensitive to streptomycin, chloramphenicol, and oxytetracycline. They inhibited the growth of corynebacteria (Parker *et al.*, 1955) and were egg-yolk negative (Gillespie and Alder, 1952).

Subsequent inquiry revealed that Nurse C had had impetigo three years previously. She had worked only in the nursery of floor 3 since her arrival, and had been in close contact with the first case. This baby had been separated from his mother for some days on account of her past history of tuberculosis, and Nurse C had been given special duties with him. Nurse C left the hospital, for personal reasons, on January 30, 1956, seven days after the outbreak of pemphigus began.

The steps taken to stop the outbreak consisted in isolation and barrier nursing of the cases and treating them with intramuscular streptomycin and local antiseptics, isolating the contacts, and autoclaving all garments and bedding of the cases and contacts and of their mothers. Most of the blankets and garments on floor 3 and many on floor 2 were thus sterilized. Admissions to floor 3 were stopped until all cases and contacts had been discharged. As an emergency measure, nose swabs were taken from all members of the nursing, domestic, physiotherapy, and resident medical staff, and from all mothers and babies in the hospital. Hand swabs were taken from some nurses, and umbilical swabs from some babies. Of the 165 swabs thus taken, 62 yielded *Staph. aureus*, but the epidemic strain was not isolated.

There were no more cases of pemphigus until March 15, 1956, when a baby on floor 3 developed a small bulla on the scalp which yielded a penicillin-sensitive type 71 staphylococcus. This may have been a variant of the epidemic strain. There have been no cases during the subsequent five months, but the epidemic strain has been isolated occasionally from other sources—a nurse's nose, a nurse's hand, a baby's nose, a baby's eye, a settle plate, and two blankets.

Since the beginning of April, all babies' garments and blankets have been disinfected by means of cetyl trimethylamine bromide ("cirrasol OD") (Blowers and Wallace, 1955).

Discussion

In several outbreaks of pemphigus neonatorum typing by sera or phages has shown the causative organisms to be particular epidemic strains of *Staph. aureus* (Elliott *et al.*, 1941; Hobbs, 1944; Allison and Hobbs, 1947; Williams *et al.*, 1947; Parker and Kennedy, 1949; Rowntree *et al.*, 1956). Our findings again illustrate the specific nature of the infection and show that it is sometimes caused by type 71 staphylococci, which in older people causes staphylococcal impetigo. The nurse who brought the organism into the hospital may have been carrying it in her nose since her own attack of impetigo three years before. A persistent nasal carrier may harbour the same strain for several years (Gould and McKillop, 1954).

The dissemination of the type 71 strain on floor 3, after Nurse C's arrival, illustrates the importance of nasal carriers in contributing staphylococci to the environment. Nevertheless, it is likely that the first case of pemphigus resulted from direct infection by Nurse C, possibly via her hands. The rapidity with which the subsequent cases followed showed that most of them were caused by cross-infection from the first case; the organisms were probably transferred by contact by members of the staff.

The transfer of organisms to floor 2, where they were found on a few occasions, may have taken place through the laundry. Case 6 may have been infected in this way.

Our experience before the outbreak of pemphigus illustrates the well-known fact that clinical staphylococcal infections are often few and mild even when there is a great deal of "bacteriological" cross-infection in a hospital (Rowntree and Barbour, 1950; Barber *et al.*, 1953; Clarke *et al.*, 1954). But the introduction of more virulent strains, or the presence of patients with lowered resistance or with wounds which expose susceptible tissues, may at any time result in serious infections. Therefore it is important to reduce staphylococcal cross-infection so far as is possible, irrespective of its clinical results at any particular time.

When an outbreak of infection is caused by a particular epidemic strain, special precautions should be taken to limit its spread. Bedclothes should be disinfected after use if this is not already being done. The oiling of blankets, which merely suppresses dust, is not enough (Clarke *et al.*, 1954). A hand cream containing a disinfectant such as chlorhexidine ("hibitane") (Murray and Calman, 1955) may be used by nurses. Affected patients should if possible be isolated and nursed by a separate staff. Nasal carriers of the epidemic strain should be detected and treated if possible. We have recently had encouraging results in a preliminary trial of "graneodin" ointment in the treatment of nasal carriers. This ointment contains gramicidin and neomycin. Its application to the nostrils four times a day for a week or two has usually cured the carrier state. E. S. Duthie (personal communication) has also had encouraging results in a more extensive trial of this method. Rowntree *et al.* (1956) have reported success in controlling neonatal staphylococcal infection by treating the noses of the staff with an ointment containing bacitracin and neomycin.

Summary

An outbreak of pemphigus neonatorum in a maternity hospital followed the introduction by a nasal carrier of *Staph. aureus* phage type 71.

For four months before the outbreak started an investigation of staphylococcal cross-infection had been conducted in the hospital, and this investigation was continued during the outbreak. It was therefore possible to detect the epidemic strain during the period which elapsed between its introduction into the hospital and the outbreak of pemphigus.

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Medical Memoranda

Fatal Thrombocytopenic Purpura Due to Quinidine

Moodie (1950) reported the first case of thrombocytopenic purpura due to quinidine in this country and reviewed five others. Since then 22 further cases have been described, all of which recovered completely. We wish to report a fatal case.

CASE REPORT

A foundry manager aged 40 had no serious illnesses until the onset of angina pectoris in September, 1955. He was away from work for four weeks following myocardial infarction in April, 1956, and was admitted to hospital on July 17 with a fresh antero-septal infarct. He was treated with heparin for 24 hours after admission and phenindione ("dindevan") for six weeks, until September 1, when he left hospital. The prothrombin index was maintained around 40, without bleeding episodes or purpura.

On his fifth day in hospital he developed paroxysmal ventricular tachycardia, for which he was given procaine amide ("pronestyl"). Because of recurrent paroxysms a total of 68 g. of procaine amide was given over the next 20 days. His leucocyte count fell from 9,700 to 3,700 per c.mm., as frequently occurs with this drug, and later returned to the normal level. When the paroxysms started he was given a test dose of quinidine followed by 5 gr. (0.32 g.) six-hourly for six days, and 10 gr. (0.65 g.) six-hourly for 37 days until he left hospital.

He was sent home on a maintenance dose of quinidine, 5 gr. (0.32 g.) three times a day. After 16 days—when he had taken a total of 1,840 gr. (119 g.)—he noticed spots on his legs, and haematuria developed two days later. We saw him on the twentieth day, stopped the drug, and readmitted him to hospital (September 21). He then had severe purpura on the face and limbs, some spots on the trunk, and macroscopic haematuria. There were no retinal haemorrhages and the spleen was not palpable. The blood pressure was 130/80.

Blood examination showed: haemoglobin, 95% (14 g./100 ml.); W.B.C., 7,500 per c.mm., with a normal differential count; platelets 56,000 per c.mm.

At 3.20 a.m. the next day he woke with dysarthria and weakness of the right arm and the right side of the face. At 5 a.m. he lost consciousness, had a severe epistaxis at 6 a.m., and died one and a half hours later.

Necropsy.—Small submucous haemorrhages were found in many viscera and in the muscles and connective tissue throughout the body, and large haemorrhages occurred in both renal pelves and in the left cerebral hemisphere. The spleen was enlarged (370 g.) and very soft. There was severe coronary atheroma with old and recent myocardial

infarction. The bone marrow appeared normal on microscopy, and megakaryocytes were numerous, but details of their morphology could not be studied in the material available.

COMMENT

The subject of quinidine purpura has been reviewed by Bolton and Dameshek (1956).

Sex and Age.—Of the 29 recorded cases only 5, including this one, were in men. This is parallel with the incidence of idiopathic thrombocytopenic purpura, which is said to be "almost wholly confined to women when the first symptoms appear in adults" (Castle, 1955). There have been no reported cases of quinidine purpura in children; most patients have been over 55 years and a few were over 70 (Collins, 1950; Lipson, 1952; Aakesson, 1952). Since quinidine is more often employed in young patients it seems that elderly women are most liable to the hazard.

Sensitizing Dose.—Purpura may occur at any stage in quinidine therapy, and in this case it appeared after eight weeks' treatment and a total dosage of 1,840 gr. (119 g.). Some patients have become sensitive after only a few days and a total dose of less than 50 gr. (3.2 g.) (Larimer, 1949; Moodie, 1950). Others have taken several hundred grains over one or two months before developing purpura for the first time. Bigelow and Desforges (1952) had a patient who had taken quinidine daily for two years before purpura appeared. In patients who have previously had quinidine purpura a test dose of 3–6 gr. (0.2–0.4 g.) has rapidly produced severe thrombocytopenia in almost all recorded cases. One exception developed fever and a rash. A patient (Norcross, 1950) who had three purpuric episodes in seven years nearly died in coma with convulsions after 9 gr. (0.6 g.); and a later test dose of 3 mg. reduced the platelets to 33,500 per c.mm. Moodie (1950) describes an unsuccessful attempt at desensitization. It thus appears that quinidine is absolutely contraindicated in patients who have had quinidine purpura.

Pathogenesis.—Platelet antibodies, defective maturation of the megakaryocytes, and capillary damage have all been implicated in the production of quinidine purpura. The extreme thrombocytopenia occurring within a few hours of a test dose of quinidine (Nussbaum and Shulman, 1952; Larson, 1953) implies destruction or removal of circulating platelets, apart from any action on the bone marrow, the usual platelet life being two to seven days. As in purpura due to "sedormid" (Ackroyd, 1949), the patient probably forms antibodies to a drug-platelet complex. The serum of these patients agglutinates normal platelets in the presence of quinidine (Bigelow and Desforges, 1952), and agglutination is followed by lysis if complement is also present (Ackroyd, 1949; Bolton and Dameshek, 1956). In essential thrombocytopenia the marrow usually contains a normal proportion of megakaryocytes, though there may be a preponderance of abnormal or immature forms, of which the appearances suggest depressed platelet formation. This latter picture is described by Hirsch and Dameshek (1950) and Phelps (1951) in cases of quinidine purpura. Marrow obtained at necropsy in the present case contained a normal proportion of megakaryocytes, but their morphological details could not be discerned. Bleeding is not simply related to the severity of thrombocytopenia, and capillary dysfunction is equally important. Ackroyd (1949) demonstrated that in susceptible patients patch tests with sedormid produce local haemorrhage and capillary fragility without thrombocytopenia. However, a patch test with quinidine was negative in Larson's (1953) case, and Bolton and Dameshek (1956) were unable to detect capillary antibodies in their cases.

Prognosis.—In 28 published cases purpura subsided within a few days of stopping the quinidine, and the platelets were normal in one or two weeks. The platelets may continue to fall for two days (Phelps, 1951). The fatal outcome in this case cannot be attributed solely to his taking quinidine for four days after the appearance of petechiae, since many other patients did this without serious consequences. One