Clinical Review

Campylobacter jejuni Septicemia—Epidemiology, Clinical Features and Outcome

VINOD K. DHAWAN, MD, FRCP(C); DAVID D. ULMER, MD; RONALD NACHUM, PhD; BHAVANI RAO, MD, *and* ROSALINA C. SEE, MD, *Los Angeles*

In 33 cases of Campylobacter jejuni *septicemia, the disease was more common at the extremes of age: infants made up a third of the reported cases while 24% of patients were older than 50 years. Fever was noted in more than 80% of patients and chills in about a fourth. Enteritis was present in 70% of cases, and the gastrointestinal tract was the principal source of septicemia. Half of the patients did not have significant underlying disease but were at extremes of age, which may reflect relative host impairment. Mortality (25%) owing to* C jejuni *septicemia occurs mostly in compromised hosts.*

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Campylobacter jejuni, formerly referred to as *Campylobacter fetus* subspecies *jejuni, Vibrio jejuni* or "related vibrios," has been recognized as an important cause of acute enteritis only since Skirrow's introduction of a selective fecal isolation medium.[1] The organism can be isolated from stools in 4% to 13.9% of patients with diarrhea[2] and, in a large multicenter study in the United States, was found more frequently in stool than either *Salmonella* or *Shigella.*[3] While *C jejuni* appears to be a frequent cause of acute enteritis, bloodstream invasion by the organism is distinctly unusual. For example, only 4 of 1,336 patients with *Campylobacter* enteritis in a series reported from Britain had bacteremia.[4] Hence, we were surprised to encounter four patients with *C jejuni* septicemia at the Martin Luther King, Jr/Charles R. Drew Medical Center, Los Angeles, during an 18-month period. The clinical features of these cases are here reviewed and compared with those of previously reported cases of this unusual disease.

Reports of Cases

Case 1

An 18-month-old female infant in previous good health was seen in December 1981 in the outpatient clinic with a history of high fever for a day and a single generalized seizure. She did not have cough, vomiting or diarrhea. No other member of the household had recently experienced a febrile or a diarrheal illness. No animal contact was identified. The child was in no apparent distress despite a temperature of 41 °C (105.8°F) rectally, a pulse of 168 and a respiratory rate of 33 per minute. The pharyngeal mucosa was slightly hyperemic but the findings of the physical examination were otherwise normal. The leukocyte count was 16,500 per μl with 48% polymorphonuclear leukocytes and 9% band forms. A chest x-ray film was normal. An upper respiratory tract infection was suspected. Specimens of blood and a throat swab were cultured and the child was discharged on a regimen of erythromycin and acetaminophen drops.

Because of the growth of *C jejuni* in blood, she was called on four days later. At that time she had been afebrile for two days and appeared well. A repeat physical examination showed no abnormalities. The throat culture had grown normal flora. Blood was recultured, the cultures remained sterile for ten days and the child was well on follow-up.

Case 2

The patient, an 1,190-gram female infant, was delivered vaginally at 29 weeks' gestation in late March 1982. Her 23-year-old mother complained of vague abdominal discomfort, water per vagina for a week before delivery and cough, fever and diarrhea that had developed three days previously. Shortly after delivery the child became apneic and cyanotic. An endotracheal tube was inserted, she was given 100% oxygen and subsequently placed on a ventilator.

The child was microcephalic. Her temperature was 38°C

From the Division of Infectious Diseases, Departments of Medicine (Drs Dhawan, Ulmer, Rao and See) and Pathology (Dr Nachum), Charles R. Drew Postgraduate Medical School and UCLA School of Medicine, Los Angeles.

Reprint requests to Vinod K. Dhawan, MD, Division of Infectious Diseases, Dept of Medicine, King/Drew Medical Center, 12021 S Wilmington Ave, Los Angeles, CA 90059.

(101°F) rectally and her heart rate 150 beats per minute. A grade 3/6 holosystolic murmur was heard and later attributed to a patent ductus arteriosus. At birth, the leukocyte count was 21,900 per μl with 9% polymorphonuclear leukocytes, 4% bands, 84% lymphocytes and 3% monocytes. Cerebrospinal fluid examination showed no abnormalities.

After blood cultures, the child received ampicillin and gentamicin sulfate intravenously. On the third hospital day, she passed three stools that were positive for occult blood using *O*-toluidine (Hematest). On the fourth hospital day, the admission blood cultures grew *C jejuni* sensitive to both antibiotics the child was receiving. Her condition improved slowly and blood specimens cultured on hospital days 7 and 8 were sterile. Antibiotic therapy was continued for ten days.

Cultures of blood specimens taken from the mother before delivery were sterile and her stools did not contain any bacterial pathogens. Endometrial cultures grew *Escherichia coli*, diphtheroids, *Staphylococcus aureus* and α-hemolytic streptococcus, but were not specifically cultured for *Campylobacter*.

Case 3

The patient, a 6-day-old female infant, the product of a full-term normal vaginal delivery, was admitted in April 1983 after three days of diarrhea and occasional vomiting but no fever. The stools contained mucus and blood. The 31-year-old mother reported a self-limited diarrheal illness a week before delivery. On physical examination on admission, the child appeared comfortable. The rectal temperature was 37.2°C (99°F), the heart rate 150 and the respirations 48 per minute. Except for the presence of an anal fissure, the physical examination showed no abnormalities.

The leukocyte count was 11,300 per μl with 27% neutrophils and 2% bands. Blood and stool specimens were obtained for culture and the child received fluids intravenously. Antibiotic therapy was withheld. No pathogens were recovered from the stools but on the sixth hospital day, *C jejuni* was found in cultures of blood specimens taken on admission. Blood was recultured and the child placed on a regimen of ampicillin, 125 mg given intravenously every six hours. No organisms were recovered from subsequent blood cultures and the antibiotic therapy was terminated four days later. The child was discharged and remained well during follow-up.

Case 4

The patient, a 62-year-old man with alcoholic cirrhosis and congestive heart failure, was admitted to hospital in mid-May 1983 because of increased shortness of breath and epigastric pain. He said he did not have vomiting, diarrhea, fever or urinary symptoms. The patient appeared ill, had jaundice and was in moderate respiratory distress. The temperature was 36°C (97°F), blood pressure 110/70 mm of mercury, respirations 29 and pulse 90 per minute. Rales were audible at the bases of both lungs but no pedal edema or jugular venous distension was noted. The heart was enlarged with a 2/6 systolic ejection murmur along the left sternal border. There was epigastric and right lower quadrant tenderness. The liver span was percussed to 16 cm.

On admission, the leukocyte count was 8,000 per μl with 49% polymorphonuclear leukocytes and 20% bands. The total serum bilirubin level was 8 mg per dl (direct 3.5); serum aspartate aminotransferase was 447 IU per liter (normal 25 to 97); total protein 5.3 grams per dl, and albumin 3.2 grams per dl. Analysis of the urine showed bile. The serum ammonia concentration was 141 μmol per liter.

The patient was thought to have decompensated alcoholic liver disease. Soon after admission, he became confused and vomited blood. His temperature rose to 37.7°C (100°F) and hypotension developed. Blood specimens for culture were taken on the day of admission, and clindamycin, 600 mg every six hours, and gentamicin, 80 mg every eight hours, were administered intravenously. Despite aggressive supportive management, the patient died on the third hospital day. The blood cultures grew *C jejuni*. Permission for autopsy could not be obtained.

Discussion

Recent classifications of the genus *Campylobacter* (family Spirillaceae) recognize three medically important species, *C fetus* subspecies *fetus* (formerly *C fetus* subspecies *intestinalis*), *C jejuni* (formerly *C fetus* subspecies *jejuni*) and *Campylobacter coli*.[5] The genus is characterized by nonsporing, thin, spirally curved rods that may appear S-shaped or gull-winged. *Campylobacter* species pathogenic for humans are microaerophilic, require oxygen concentrations ranging from 5% to 15% and grow neither aerobically nor anaerobically. The organisms are motile with a single polar flagellum at one of both ends.

In our laboratory, isolation of *C jejuni* from fecal material was done on Campy-BAP, a selective medium.[6] Plates were incubated in a 42°C incubator in a GasPak jar with a disposable gas generator (CampyPak) to produce atmospheres suitable for growth. Isolation of *C jejuni* from blood was done in supplemented tryptic soy broth (BACTEC culture vials 6B and 7D) using a radiometric detection system (BACTEC). Preliminary identification of the genus *Campylobacter* was done by microscopic examination of Gram-stained preparations, either from colonies or from blood cultures, and positive oxidase and catalase tests. Specific identification of *C jejuni* was based on growth at 42°C and sensitivity to nalidixic acid (30 μg per disc), the latter done on noninhibitory blood agar.[7]

Campylobacter infections, long known as an important cause of animal disease, have been recognized in humans only since 1947.[8] Before 1972, bacteremia was the only frequent form of human infection identified,[9] due to the unavailability of selective media to prevent overgrowth of *Campylobacter* by the coliforms when stools were cultured. Guerrant and co-workers reviewed the 91 cases of *Campylobacter* bacteremia that had been reported up to 1978, and only ten were due to *C jejuni*.[10] *Campylobacter fetus* subspecies *fetus*, the other human pathogenic species, is found in blood with much greater frequency than *C jejuni* but is rarely isolated from the feces of infected patients.[11] While *C jejuni* septicemia has been reported more frequently during the past five years, it remains a rare condition and our encounter with four such patients over an 18-month period is noteworthy.

Epidemiology of C jejuni *Septicemia*

Although septicemia due to *C jejuni* has been reported in all age groups, the incidence appears to be increased during infancy and in older age. Of 33 cases reviewed here, 12 of the

patients (36%) were younger than a year whereas 8 (24%) were older than 50 years (Table 1). There is no predilection for either sex nor has any racial predisposition been described. In two of our patients, *C jejuni* septicemia developed soon after birth. Little is known about the transplacental transmission of *C jejuni*, although a case of midtrimester abortion and placentitis due to *C jejuni* has been reported.[12] The placentas of both of our neonates appeared normal and, therefore, specimens were not taken for culture. The mothers of both infants, however, had diarrhea during the peripartum period. Hence, even in the absence of microbiologic proof, it is tempting to speculate that infection was acquired during delivery from the contaminated maternal birth canal.

Half of the patients with *C jejuni* septicemia did not have any significant underlying disease (Table 1). Two patients, however, were pregnant at the time they acquired the infection and septicemia developed in another within 42 hours postpartum. Three infected children were born prematurely

TABLE 1.—*Clinical Features in Reported Cases of* Campylobacter jejuni *Septicemia*

Case	Age	Sex	Underlying Condition	Fever	Diarrhea	Treatment	Outcome	Reference No.
1	3 mo	♀	Unidentified rash	Absent	Present	Sulfisoxazole (Gantrisin)	Recovered	13
2	5 yr	♂	Chronic ear infection, osteomyelitis of knee and wrist	?	Present	Tetracycline hydrochloride (Achromycin)	Recovered	13
3	2 mo	♂	Hydrocephalus	Present	Present	Penicillin, tetracycline	Recovered	13
4	2 mo	♂	None	Absent	Present	?	Recovered	13
5	11 mo	?	Recent measles	Present	Absent	Penicillin, streptomycin	Recovered; stool culture negative	14
6	2 mo	♀	None	Absent	Present*	Chloramphenicol	Recovered; stool culture negative	15
7	1 mo	♀	None	Present†	Present	Chloramphenicol, streptomycin	Recovered; stool culture negative	16
8	28 yr	♂	Cirrhosis of liver, perforated duodenal ulcer	Present	Present	Chloramphenicol, streptomycin	Died; stool culture negative	17
9	22 yr	♀	Asthma	Present	Present*	Chloramphenicol	Recovered; stool culture positive	18
10	21 mo	♀	Kwashiorkor	Absent	Present	Penicillin, streptomycin, kanamycin sulfate, ampicillin	Recovered	19
11	8 d	♀	Jaundice	?	Present	Penicillin, kanamycin	Died soon after admission	19
12	26 yr	♂	None	Present†	Present*	Penicillin, erythromycin	Recovered	20
13	67 yr	?	Waldenstrom's disease, steroid therapy	Present†	Absent	Erythromycin, ethambutol hydrochloride (Myambutol)	Died; blood transfusion was the source	21
14	25 yr	♀	Postpartum	Present	Present	Ampicillin	Recovered	22
15	14 yr	♂	Acute lymphocytic leukemia	Present	Present	Ampicillin	Recovered	22
16	14 yr	♂	None	Present	Present	None	Recovered	22
17	68 yr	♂	Chronic hydradenitis	Present	Present*	None	Recovered; stool culture negative	23
18	23 yr	♀	Pregnancy	Present†	Absent	Cephalothin, metronidazole, cephalexin	Recovered; aborted	12
19	1 d	♂	Prematurity	Present	Absent	Kanamycin, erythromycin, penicillin	Died; possibly caused prematurity; mother's stool culture positive	24
20	56 yr	♀	None	Present	Present	Ampicillin	Recovered; the isolate was resistant to β-lactam antibiotics	25
21	11 yr	♀	None	Present†	Present	None	Recovered	25
22	74 yr	♂	Thymoma, malabsorption, hypoplastic anemia	Present†	Absent	Penicillin, ampicillin, gentamicin sulfate	Recovered	25
23	66 yr	♂	Chronic bronchitis	Present	Present	Penicillin	Recovered; isolate resistant to penicillin; stool culture positive	25
24	51 yr	♂	Peptic ulcer disease, repeated pneumonia	Present†	Present	Ampicillin	Recovered; isolate resistant to ampicillin; stool culture negative	25
25	79 yr	♂	None	Present†	Present	Cephalosporin, gentamicin, tetracycline	Recovered; stool culture negative	26
26	40 yr	♂	Mixed histiocytic lymphoma	Present	Absent	Erythromycin	Died	27
27	48 yr	♂	Diffuse lymphocytic lymphoma	Present	Absent	Chloramphenicol, gentamicin, cephalothin	Died	27
28	1 mo	♂	Prematurity	Present	Present	Gentamicin	Died	28
29	4 mo	♀	None	Present	Present	Penicillin	Recovered	28
30	18 mo	♀	None	Present	Absent	Erythromycin	Recovered	This report, case 1
31	1 d	♀	Prematurity	Present	Present*	Ampicillin, gentamicin	Recovered; mother had diarrhea	This report, case 2
32	62 yr	♂	Alcoholic cirrhosis	Present	Absent	Clindamycin, gentamicin	Died	This report, case 3
33	6 d	♀	None	Present	Present*	Ampicillin	Recovered; stool culture negative	This report, case 4

*Blood present in stools.
†Chills were present.

while two adults in addition to our patient had cirrhosis of liver. Two patients had lymphoma and one each had acute lymphocytic leukemia, Waldenstrom's disease, thymoma, kwashiorkor, recent history of measles and chronic hydradenitis.

C jejuni is a pathogen or a commensal in several animals (cattle, sheep, swine, poultry, cat and dog), and food, milk, water and sick animals are the major sources of infection.[29] Contact with animals, however, was reported in only four of the patients described thus far, one case each with a cat,[21] dog,[15] horse[26] and snake.[19] Ingestion of chicken and tuna salad was implicated in one patient, although the organism was not recovered from food.[22] Perinatal campylobacteriosis is most commonly due to *C fetus* subspecies *fetus* and very rarely due to *C jejuni*.[30]

Clinical Features of C jejuni *Septicemia*

About 70% of patients with *C jejuni* septicemia have enteritis that is presumed to be the source of septicemia. These patients present with symptoms of abdominal pain and diarrhea and with blood in the stool in a third of the cases. While the organism was recovered from stool in only 3 of 21 patients with enteritis summarized in Table 1, most either lacked stool cultures or were studied before the development of selective fecal isolation media. In 30% of reported cases, including two of our patients, diarrhea was not present and the source of infection remains speculative. In one patient, however, the disease was probably acquired through a blood transfusion.[20]

Fever is an important feature of *C jejuni* septicemia and is present in more than 80% of patients. Approximately a fourth of such febrile patients experience chills. Other symptoms may include malaise, nausea, vomiting and headache. The leukocyte count is frequently elevated but generally below 20,000 per μl. The recovery of organisms from blood may take from 24 hours[14] to 9 days.[19]

Treatment and Outcome of C jejuni *Septicemia*

The natural history of *C jejuni* septicemia depends on the premorbid state of the host. In the absence of serious underlying disease, *C jejuni* septicemia appears to run a benign course. Of the 33 reported patients, however, 8, all compromised hosts, died (Table 1). All of these patients had received antibiotics to which the organisms were later found to be susceptible. Nonfatal but serious complications of *C jejuni* septicemia are few: the disease has been implicated as the cause of abortion in one patient[12] and of premature labor in another.[24]

Most patients with *C jejuni* septicemia have been treated empirically with one or more antibiotic drugs. In three reported cases, however, the patients recovered without antibiotic therapy and four others responded even though the organism was found to be resistant to the antibiotic used (Table 1). In vitro susceptibility testing of 24 antimicrobials against 86 strains of *C jejuni* show the penicillins to have poor activity,[31] whereas erythromycin and the aminoglycosides, such as gentamicin, tobramycin and amikacin, were the most active and should be considered the agents of choice. Chloramphenicol is also active and should be considered in patients in whom central nervous system involvement such as meningitis may be present. All four strains isolated from our patients were sensitive to erythromycin, chloramphenicol, gentamicin, tobramycin and amikacin but resistant to penicillin, cephalothin and methicillin.

Despite the prevalence of *C jejuni* in patients with infectious diarrhea and the tendency to intestinal wall invasion by this organism, isolation of *C jejuni* from blood specimens is remarkably infrequent. There may be several reasons for this circumstance. Blood cultures may not be done routinely in patients with diarrhea unless they appear septic. Alternatively, the bacteremia may occur early and be missed in blood specimens taken late in the course of the disease.[30] Failure to use specific media and the proper temperature necessary—that is, 42°C for the growth of *C jejuni*—may be another cause of negative blood cultures. More recently, complement-mediated killing of *C jejuni* by serum has been implicated to explain the infrequency of bacteremia due to this organism.[32]

Campylobacter jejuni septicemia should be considered in the differential diagnosis of febrile patients especially in the presence of enteritis. The blood cultures should be incubated for as long as ten days and subcultured on agar slants conducive to growth of this organism at 42°C. Early recognition of systemic infection and prompt intervention with appropriate antibiotics should favorably alter the course of *C jejuni* septicemia and is likely of critical importance in a compromised host.

REFERENCES

1. Skirrow MB: *Campylobacter* enteritis—A 'new' disease. Br Med J 1977; 2:9-11
2. Rettig PJ: *Campylobacter* infections in human beings. J Pediatr 1979; 94:855-864
3. Blaser MJ, Wells JG, Feldman RA, et al: *Campylobacter* enteritis in the United States—A multicenter study. Ann Intern Med 1983; 98:360-365
4. *Campylobacter* infection in Britain, 1977. Br Med J 1978; 1:1357
5. Skerman VBD, McGowan V, Sneath PHA: Approved lists of bacterial names. Int J System Bacteriol 1980; 30:225-420
6. Blaser MJ, Berkowitz ID, La Force FM, et al: *Campylobacter* enteritis: Clinical and epidemiologic features. Ann Intern Med 1979; 91:179-185
7. Koneman EW, Allen SD, Dowell VR Jr, et al: Color Atlas and Textbook of Diagnostic Microbiology, 2nd Ed. Philadelphia, JB Lippincott, 1983, pp 188-192
8. Vinzent R, Dumas J, Picard N: Septicemie grave an cours de la grossesse, due a un vibrion—Avortement consecutif. Bull Acad Natl Med (Paris) 1947; 131:90-92
9. Bokkenhenser V, Dunstom T: Vibrio fetus infections in man: Occurrence, clinical picture, serology and source of infections, *In* Von Graevenitz A, Sall T (Eds): Microorganisms and Infectious Diseases, Vol 1. New York, Marcel Dekker, 1975, p 25
10. Guerrant RL, Lahita RG, Winn WC, et al: Campylobacteriosis in man—Pathogenic mechanisms and review of 91 blood stream infections. Am J Med 1978; 65:584-592
11. Blaser MJ, Wang WL: *Campylobacter* infections in human beings (Letter). J Pediatr 1980; 96:343
12. Gilbert GL, Davoren RA, Cole ME, et al: Midtrimester abortion associated with septicemia caused by *Campylobacter jejuni*. Med J Aust 1981; 1:585-586
13. King EO: Human infections with *Vibrio fetus* and a closely related vibrio. J Infect Dis 1957; 101:119-128
14. Wheeler WE, Borchers J: Vibrionic enteritis in infants. Am J Dis Child 1961; 101:60-66
15. Middlekamp JN, Wolf HA: Infection due to a 'related' vibrio. J Pediatr 1961; 59:318-321
16. Ruben FL, Wolinsky E: Human infection with *Vibrio fetus*. Antimicrob Agents Chemother 1967; 7:143-149
17. Darrell JH, Farrell BC, Mulligan RA: Case of human vibriosis. Br Med J 1967; 2:287-289
18. Dekeyser P, Gossuin-Detrain M, Butzler JP, et al: Acute enteritis due to a related vibrio: First positive stool cultures. J Infect Dis 1972; 125:390-392
19. Hallett AF, Botha PL, Logan A: Isolation of *Campylobacter fetus* from recent cases of human vibriosis. J Hyg 1977; 79:381-389
20. Longfield R, O'Donnell J, Yudt W, et al: Acute colitis and bacteremia due to *Campylobacter fetus*. Dig Dis Sci 1979; 24:950-953
21. Pepersack F, Prigogyne T, Butzler JP, et al: *Campylobacter jejuni* post-transfusional septicaemia (Letter). Lancet 1979; 2:911
22. Taylor PR, Weinstein WM, Bryner JH: *Campylobacter fetus* infection in human subjects: Association with raw milk. Am J Med 1979; 66:779-783
23. Eiden J, Moseley G, Dalton HP: *Campylobacter fetus* subspecies *jejuni* bacteremia. South Med J 1980; 73:1092-1093
24. Miller RC, Guard RW: A case of premature labour due to *Campylobacter jejuni* infection. Aust NZ J Obstet Gynecol 1982; 22:118-120

25. Walder M, Lindberg A, Schalén C, et al: Five cases of *Campylobacter jejuni/coli* bacteremia. Scand J Infect Dis 1982; 14:201-205

26. Schwartz JN, Stamper LL: Acute *Campylobacter* gastroenteritis and bacteremia. NC Med J 1979; 40:505-507

27. Longfield RN, Crane JM, Pasquale DN: *Campylobacter fetus* subsp *jejuni* bacteremia in diffuse lymphoma. Mayo Clin Proc 1981; 56:582-583

28. Puthucheary SD, Lin HP: Bacteraemic enteritis due to *Campylobacter jejuni*. Med J Malaysia 1982; 37:378-380

29. Butzler JP, Skirrow MB: Campylobacter enteritis. Clin Gastroenterol 1979; 8:737-765

30. Trophy ET, Bond WW: *Campylobacter fetus* infections in children. Pediatrics 1979; 64:898-903

31. Vanhoof R, Gordts B, Dierickx R, et al: Bacteriostatic and bactericidal activities of 24 antimicrobial agents against *Campylobacter fetus* subsp *jejuni*. Antimicrob Agents Chemother 1980; 18:118-121

32. Pennie RA, Pearson RD, Guerrant RL: Sensitivity of *Campylobacter jejuni* to killing by human serum (Abstr). Clin Res 1983; 31:849A

Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Permanent Eyeliner

QUESTION:

Is the application of permanent eyeliner considered to be accepted medical practice?

OPINION:

While the preliminary experience with permanent eyeliner indicates that its application appears safe and without serious complications, it is the opinion of the Scientific Advisory Panels on Ophthalmology and Plastic Surgery that further clinical investigation is needed to determine the long-term results of this procedure, particularly freedom from allergic blepharitis and eyelash depilation, before it can be considered established medical practice. The application of permanent eyeliner is clearly a cosmetic procedure and one that has been growing in popularity over the last few years. For women with poor vision, or who are allergic to commercially available cosmetics, or who have disabilities that prevent them from applying topical cosmetics, permanent tattooing of the eyelids may be beneficial. In cases of eyelid disease or trauma, it could be part of a reconstructive plastic surgical plan where such enhancement of the eyelids or brows or both is indicated.

The advisory panels acknowledge that tattooing has been commonly done outside the medical profession for many years and that long-term results have been good, provided aseptic techniques have been used. Though relatively new, permanent eyeliner application, which is fundamentally no different from other tattooing procedures, is being widely done and, in the hands of physician specialists properly trained in the technique, the complication rate is reported to be extremely low. The advisory panels are not aware of published scientific evidence, however, that documents the safety of this procedure over a long period of time. The advisory panels will periodically review this question as such information becomes available.