THE NEUROPATHOLOGIC COMPLICATIONS OF NARCOTICS ADDICTION*

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SEVERAL recent inquiries into the medical complications of narcotics addiction have reported the biologic events which follow intravenous injection of unpredictable amounts of contaminated drugs.[1-4] In Louria's analysis of 100 illnesses which had occurred in 96 addicts, 91 were infectious; an overdose of the narcotic was responsible for the remainder.[1]

A low incidence of neurologic complications in the drug addict has characterized the series of Helpern and Rho[2] and Cherubin.[3] In Louria's review of the literature, involvement of the brain was found in only nine of the 48 addicts who had developed bacterial endocarditis.[1]

The autopsy files of the neuropathology laboratory, Kings County Hospital Center, Brooklyn, N.Y., contain the records of 11 patients autopsied between 1959 and 1968 who had been identified as having been addicted to narcotics. In this small series of cases, the frequency of organic disease of the nervous system related to the use of narcotics was higher than anticipated. Nine of these 11 patients revealed abnormalities of the central nervous system at the time of autopsy; in six cases this abnormality was related to the cause of death. Seven of the 11 patients died of infectious disease. Of these seven, six showed lesions in the central nervous system. The data are summarized in Table I.

In all but one instance the diagnosis of narcotics addiction was based

*Presented at a combined meeting of the Section on Neurology and Psychiatry, the New York Neurological Society, and the New York Society of Neurosurgery, March 12, 1968.
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TABLE I. PATIENTS WITH NARCOTICS ADDICTION STUDIED AT AUTOPSY AT KINGS COUNTY HOSPITAL (1959 TO 1967)

Case No.	*Age*	*Sex*	*Narcotic used*	*Presenting symptom*	*Cause of death*	*Duration of terminal hospital stay*
1	27	M	Heroin	Fever	Bacterial endocarditis	Unknown
2	30	M	Heroin	Fever, petechiae	Bacterial endocarditis	27 days
3	26	M	Heroin	Ankle edema	Bacterial endocarditis	30 days
4	28	M	Heroin	Chest pain, dyspnea	Bacterial endocarditis	14 days
5	24	M	Heroin	Unknown	Phycomycetosis of brain	Dead on arrival
6	31	F	Heroin	Jaundice	Posthepatitic cirrhosis of liver	13 days
7	37	M	Heroin	Unknown	Tetanus	Unknown
8	26	M	Heroin	Coma	Overdose of heroin	7 days
9	42	M	Heroin	Jaundice, nausea, and vomiting	Uremia, fatty liver	5 days
10	66	M	Heroin	Dyspnea	Myocardial infarct	31 days
11	55	F	Morphine	Psychotic dementia	Pulmonary emboli	8 days

upon both the patient's own assertion that he was, in fact, addicted to narcotics, as well as upon independent corroboration from the next of kin or from prior hospital records. In the single exception (Case 5), numerous scars characteristic of needle tracts were noted on the arms at autopsy. In addition, heroin had been found in the patient's bedroom.

Each brain was cut in the coronal plane at intervals of 1 cm. Blocks of tissue for histologic study were obtained from the frontal lobe, hippocampus, basal ganglia, hypothalamus, midbrain, pons, cerebellum, and medulla in each case. Spinal cord, peripheral nerve, dura mater, and skeletal muscle were also examined when available. Additional sections were obtained when indicated.

FINDINGS

Bacterial endocarditis. Bacterial endocarditis constituted the single most frequent cause of death in this series (four cases). *Staphylococcus*

aureus (coagulase positive) was cultured antemortem from the blood in three of these four cases, while *Flavobacter* was cultured antemortem from the blood of the fourth patient.

Case 1. A 27-year-old male addict was admitted to the hospital with delirium and high fever. Several blood cultures were positive for *S. aureus.* A lumbar puncture disclosed uniformly bloody fluid which was under increased pressure. The patient died three days after admission. Autopsy disclosed acute ulcerative bacterial endocarditis *(S. aureus)* involving the aortic valve, with septic embolization to both kidneys, the spleen, and the right middle cerebral artery. The last had resulted in the formation of a mycotic aneurysm and secondary focal leptomeningitis. In addition there were many microscopic abscesses in the cerebrum and brain stem, as well as a circumscribed brain abscess, measuring about 3 cm. in greatest dimension, within the left parietal lobe.

Case 2. A 30-year-old male heroin addict was admitted to the hospital with a history of severe chills and fever, which had begun about three days previously. The patient described swelling and severe pain in his left ankle, as well as red, painless blotches on both lower extremities. Physical examination on admission disclosed a desperately ill male with numerous purpuric areas on the lower extremities. Hepatosplenomegaly was observed, as was a harsh, systolic cardiac murmur, heard best at the apex of the heart. A blood culture ultimately grew *S. aureus.* Despite vigorous antibiotic therapy the patient died. Autopsy examination confirmed the existence of acute bacterial endocarditis, which had involved the aortic and tricuspid valves, with perforation of the leaflets.

No gross changes were seen in the brain. However, large numbers of microabscesses disseminated throughout the central nervous system were observed microscopically. These focal suppurative lesions rarely exceeded the diameter of a high-power microscopic field, and seemed to be oriented about small septic emboli in terminal vessels. The surrounding neural parenchyma exhibited varying degrees of rarefaction and gliosis.

Case 3. The patient was a 26-year-old female, previously identified as a heroin addict, who was admitted to a neighboring hospital because of signs suggestive of pneumonia. The patient was transferred to this hospital, where blood cultures disclosed the existence of staphylococcal bacteremia. During a course of intensive antibiotic treatment, both systolic and diastolic murmurs evolved; these were associated with cardiac

arrhythmias. The patient did not respond to the antibiotics and died 45 days after admission. Autopsy disclosed the existence of acute bacterial endocarditis involving the tricuspid valve. Examination of the brain showed numerous foci of metastatic suppuration in the leptomeninges.

Case 4. The patient was a 28-year-old male who entered Kings County Hospital because of chest pain which had begun 10 days before admission. The patient had previously been hospitalized for the treatment of pneumonia and overdoses of heroin.

Examination on admission disclosed a moderately alert, febrile male complaining of precordial pain. The examiners noted a precordial, systolic, ejection murmur radiating to the neck, as well as a diastolic blowing murmur which was loudest at the base of the heart. No neurologic abnormalities were noted. Blood cultures on four successive occasions disclosed the presence of *Flavobacter.* In the succeeding few weeks, despite appropriate antibiotic therapy, the patient showed evidence of increasing cardiomegaly, and progressive aortic insufficiency which culminated in congestive heart failure. He died 45 days after admission. Autopsy confirmed the existence of acute bacterial endocarditis of the aortic valve. Permission was not given for examination of the brain.

In all three patients with bacterial endocarditis whose brains were examined, disseminated infection of the central nervous system was found. In two cases, this took the form of numerous perivascular collections of polymorphonuclear leukocytes within small, rarefied zones of brain tissue. The lesions were centered about capillaries or smaller venules; the central vessel often contained a small septic embolus or bacterial colony. These disseminated microabscesses represented a hematogenous spread of infected microemboli arising from the septic vegetations on the cardiac valves. In the patient with tricuspid valvulitis (Case 2) the intracranial infection was limited to the leptomeninges and assumed the form of focal, purulent leptomeningitis with localized phlebitis and venous thrombosis.

These four cases exhibit most of the possible neuropathologic sequelae of bacterial endocarditis. The organisms cultured from the blood are somewhat unusual when contrasted with the spectrum of etiologic agents recovered from the group of nonaddicts with bacterial endocarditis. They are somewhat similar to the organisms recovered from previously reported cases of bacterial endocarditis in addicts. The agents in previous

cases have included *Candida*,[5-9] *Aerobacter aerogenes*,[10] and *Staphylococcus aureus* or *Staphylococcus albus*.[11, 12]

Only one of these four patients had a preexisting rheumatic valvular disorder. The remaining three presented none of the usual pathologic stigmata of rheumatic valvulitis. The left side of the heart was involved in two of the present cases, the right side in one case; in the fourth case both sides were involved. Few neurologic symptoms were described in the clinical charts of these four patients although disseminated septic infarcts of the brain were found at autopsy. It might be noted here that disseminated intracranial microabscesses frequently produce symptoms which are mild, evanescent, and nonfocal, and that these symptoms may easily be overshadowed by the profound changes of terminal illness involving other organ systems.[13]

In previously reported cases of narcotic addiction examined at autopsy, the cerebral changes have been described only when judged to be significant. Winkler *et al.*, however, reported a case in which "near apparently occluded capillaries in the brain parenchyma there were small areas of destruction in the ground substance with few microglia and astrocytes."[7] This is identical to the histologic appearance of healing microabscesses that we have seen in patients who had sustained repeated showers of small, infected emboli.

Phycomycetosis. Infection of the nervous system caused by one of the phycomycetes occurs typically as a complication of poorly controlled diabetes mellitus. The infection usually originates in the nasal cavities, with invasion of the submucosal tissues of the nasal turbinates. The infective agent, most commonly a mucor or a rhizopus, reaches the paranasal sinuses via the veins draining the turbinates. The retroorbital tissues are characteristically involved, with edema and inflammation, and a mycotic phlebothrombosis. The infection reaches the cranial cavity by way of the communicating veins, occasionally via the branches of the internal carotid artery, and sometimes within the parenchyma of the cranial nerves. Much of the ultimate damage caused by the infection is the result of arterial and venous thromboses provoked by the presence of the organisms within the vascular walls.

*Case 5.** The patient was a 24-year-old white male who was dead upon arrival at the hospital. The patient had been a known narcotic

*This case was examined through the courtesy of Dominick DiMaio, M.D., deputy chief medical examiner, City of New York.

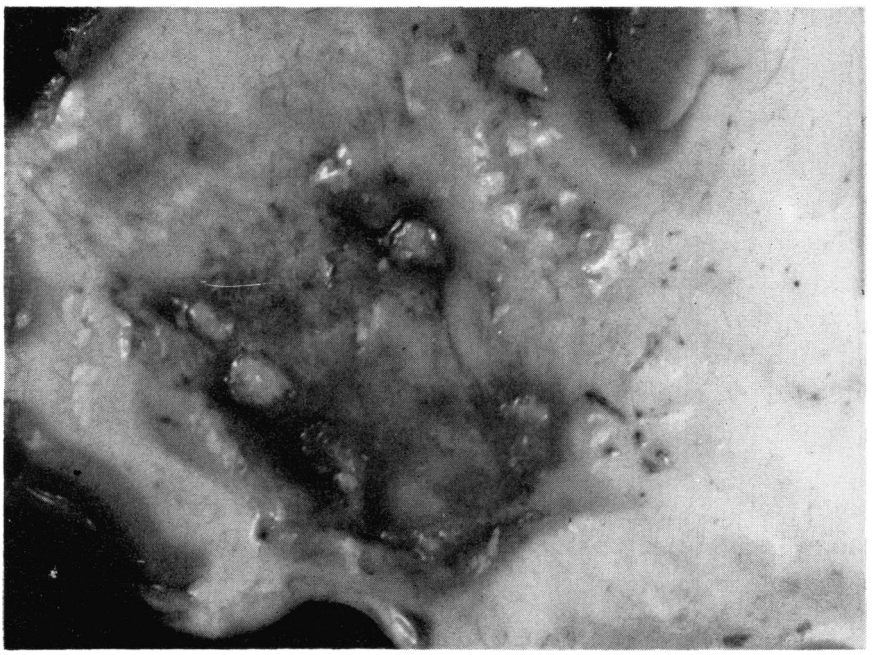

Fig. 1. Cross-section of right cerebral hemisphere (Case 5) showing a softened lesion measuring 3 cm.

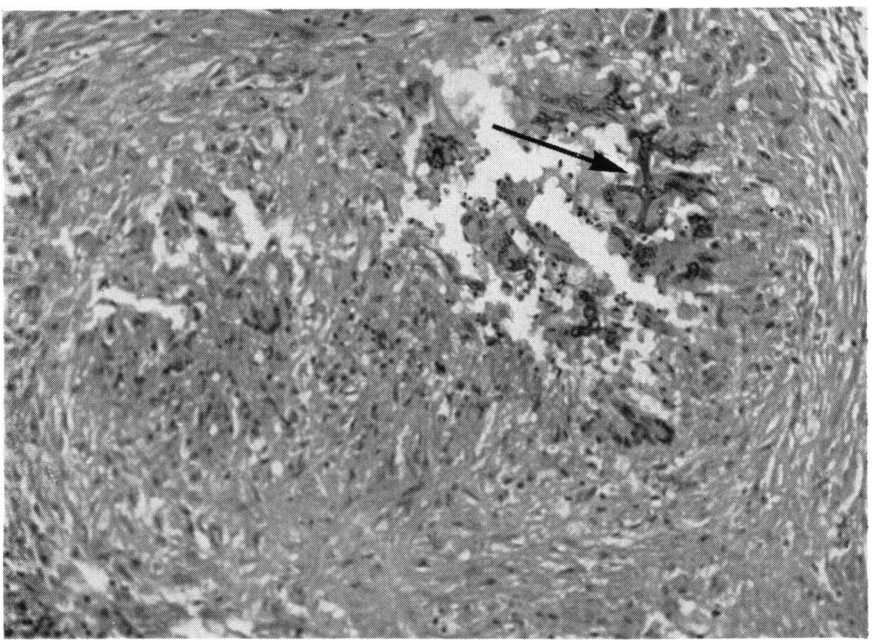

Fig. 2. Photomicrograph of necrotic cerebral tissue shown in Fig. 1, exhibiting pleomorphic granulomatous response and occasional phycomycetes (*arrow*). Hematoxylin and eosin. ×200.

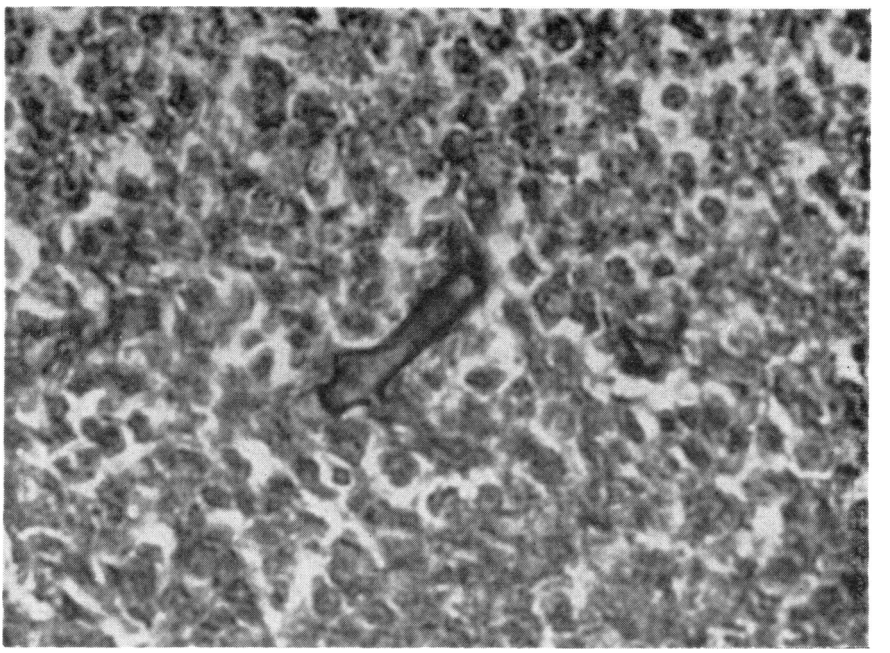

Fig. 3. Higher magnification showing nonseptate hypha in midst of inflammatory exudate. Periodic Acid-Schiff stain. ×470.

addict for many years. Conversation with his family physician revealed no evidence suggestive of diabetes mellitus, or any other factor, such as kidney disease, capable of causing acidosis.

An autopsy was performed. Needle scars were found in antecubital skin of both arms. The major changes noted at autopsy were confined to the nervous system. There was a circumscribed grayish-yellow, granular, irregularly necrotic lesion within the right basal ganglia that measured 3 cm. in diameter and approximately 1.5 cm. in rostrocaudal dimension. The lesion was located approximately at the level of the genu of the corpus callosum and extended caudally to the level of the hypothalamus, which it involved at its periphery (Figure 1). Histologically the lesion was seen to consist of confluent granulomata showing central necrosis and many reactive giant cells of the Langhans type (Figure 2). Numerous branching, nonseptate, hematoxylinophilic tubular bodies of irregular width were seen within the granulomata. The bodies are characteristic of the hyphae of the phycomycetes. They stained positively with the periodic acid-Schiff technique as well as with

Gomori's methenamine silver procedure (Figure 3). In some sections of the large mycotic abscess the characteristic affinity of these organisms for the walls of veins was demonstrated. Examination of sections from other parts of the nervous system as well as the abdominal and thoracic viscera showed no other foci of phycomycetosis.

Virtually all reported cases of verified phycomycetosis of the nervous system have arisen against a background of poorly controlled diabetes mellitus or other metabolic circumstance, such as chronic renal disease associated with acidosis. Phycomycetosis of the nervous system has not been reported previously as a complication of narcotics addiction, to the best of our knowledge. It is presumed that the present case represents an instance of fungemia similar to that seen in disseminated candidiasis[14] with persistence of the organism only in those tissues affording a locally favorable environment. The source of the infection in this case is unknown, but it may have been derived from a contaminated hypodermic needle or from the skin.

Other infectious diseases. One patient (Case 6) died of infectious hepatitis. This was a 31-year-old male who had been an addict for more than 10 years. During the decade prior to his death the patient had experienced a number of episodes of jaundice and, about four years before death, he developed massive hematemesis from ruptured esophageal varices. A portocaval shunt was established and his health improved. On his terminal admission the patient was profoundly confused, lethargic, and jaundiced. He died 13 days after admission. The nervous system showed no gross abnormalities. Many Alzheimer type II astrocytes were seen throughout the brain.

Case 7 represents a 37-year-old male drug addict who died of tetanus. The tissues of the nervous system showed only focal, nonspecific, hypoxic changes, particularly in the frontal cortex.

Further cases. Severe hypoxic changes with acute encephalomalacia involving the bilateral basal ganglia and subcortical white matter were found in the brain of Case 8, a 26-year-old male who died of an overdose of heroin. The lungs of this patient showed the characteristic hemorrhagic edema found in the cases of narcotics overdosage described by Helpern and Rho.[2]

Case 9 in this series was a 42-year-old male who was a chronic alcoholic, as well as a narcotics addict. He was admitted after a three-week illness characterized by a progressive jaundice and increasing

lethargy. Upon admission the patient showed signs of impending hepatic coma. He died on the fifth hospital day. Autopsy disclosed severe fatty changes of the liver, as well as chronic Wernicke's encephalopathy involving the mammillary bodies.

Case 10 was a patient admitted because of severe dyspnea. For 20 years he had been an acknowledged heroin addict. Five years before the present admission he had voluntarily submitted himself to hospitalization for the cure of this addiction. He stated that he had not used narcotics for the past five years. He died 31 days after admission to the hospital. Autopsy disclosed massive myocardial infarction. The central nervous system showed no abnormalities.

Case 11 was a 55-year-old female who had a 27-year history of tabes dorsalis associated with severe gastric crises. The patient had used morphine to relieve the pain of these crises and had become addicted to this drug. Upon admission to the hospital she was described as emaciated, partially paralyzed, and psychotic. Eight days after admission there was a sudden onset of dyspnea and evidence of peripheral vascular collapse. She died within three hours of the onset of these symptoms. Autopsy showed the presence of massive pulmonary emboli. Examination of the nervous system verified the presence of chronic tabes dorsalis; no other changes were seen.

Summary

The tissues of the central nervous system are described in 11 patients who were addicted to narcotics.

Bacterial endocarditis appears here to be the most common cause of death; in the central nervous system, metastatic foci of infection were found in the three cases in which the brain was examined.

A patient with granuloma of the brain due to phycomycetosis is described.

Fatty degeneration of neurons, previously described[15, 16] in association with narcotic addiction, was not observed. Indeed, no lesions characteristic of the addictive state per se were found.

REFERENCES

1. Louria, D. B., Hensle, T. and Rose, J. The major medical complications of narcotics addiction. *Ann. Intern. Med. 67*:1, 1967.
2. Helpern, M. and Rho, Y. Deaths from narcotism in New York City. *New York J. Med. 66*:2391, 1966.
3. Cherubin, C. E. The medical sequelae of narcotics addiction. *Ann. Intern. Med. 67*:23, 1967.

4. Briggs, J. H. *et al.* Severe systemic infections complicating "mainline" heroin addiction. *Lancet 2*:1227, 1967.
5. Henderson, J. and Nickerson, J. F. Bacterial endocarditis with *Candida albicans* superinfection. *Canad. Med. Ass. J. 90*:452, 1964.
6. Zimmerman, L. E. *Candida* and aspergillis endocarditis. *Arch. Path. 50*:591, 1950.
7. Winkler, A. *et al.* Mycotic endocarditis, Report of a case. *J.A.M.A. 119*:333, 1942.
8. Wilson, R. M. Candidal endocarditis. *J.A.M.A. 177*:332, 1961.
9. Andriole, V. T. *et al.* Candida endocarditis. *Amer. J. Med. 32*:251, 1962.
10. Luttgens, W. F. Endocarditis in "main line" opium addicts. *Arch. Intern. Med. 83*:653, 1949.
11. Wilhelm, F. *et al.* The treatment of acute bacterial endocarditis with penicillin. *Ann. Intern. Med. 26*:221, 1947.
12. Romansky, J. J. and Holmes, J. R. Successful short-term therapy of enterococcal and staphylococcal endocarditis with ristocetin. Seven patients. Preliminary report. *Antibiotics Annual*, 1957-1958, p. 187.
13. Sher, J. H. *et al.* Disseminated microabscesses of the central nervous system. *J. Neuropath. Exp. Neurol. 24*: 175, 1966.
14. Straatsma, B. R. *et al.* Phycomycetosis: A clinicopathological study of 51 cases. *Lab. Invest. 11*:963, 1962.
15. Weimann, W. Gehirnveränderungen bei akuter und chronischer Morphiumvergiftung. *Z. Ges. Neurol. Psychiat. 105*: 705, 1926.
16. Creutzfeld, H. G. Histologischer befund bei morphinismus mit morphiumund veronalvergiftung. *Z. Ges. Neurol. Psychiat. 101*:97, 1926.