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Stroke associated with addiction to heroin[1]

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SYNOPSIS During a five year period at the Harlem Hospital Center nine heroin addicts were seen with strokes. Four occurred after loss of consciousness following intravenous heroin. Two occurred in patients using heroin at the time, but were not related to overdose or to a particular recent injection. The youth of these patients and lack of other predisposing factors suggests that heroin played a role in their strokes. In the other three patients, the relationships of stroke to heroin is less persuasive. There are several possible mechanisms by which heroin abuse could lead to stroke.

A variety of medical (Louria *et al.*, 1967) and neurological (Richter *et al.*, 1973; Richter and Pearson, 1975) complications of addiction to heroin have been described. We give details of nine heroin addicts who were evaluated for stroke at Harlem Hospital during a five year period.

CASE 1

In August 1967, a 31 year old heroin addict injected himself intravenously with more than his usual amount of heroin. He became unresponsive for several hours and awoke with left arm and leg weakness. At another hospital his blood pressure was 150/60 mmHg, pulse 64/min and regular, respirations 15/min and regular, and temperature 37°C. There was flaccid weakness of his left arm and leg, with normal mentation and gross visual fields. Sensory examination was not reported. The rest of the physical examination was normal. Haematocrit, white blood count, urinalysis, fasting blood sugar, blood urea nitrogen, serum VDRL, cerebrospinal fluid, serum albumin and globulin, serum lactic dehydrogenase, serum aspartate aminotransferase, serum alanine aminotransferase, and skull radiographs were normal. Electroencephalography showed right frontotemporoparietal slowing. Within a few days the strength improved in his left arm and leg, but there emerged a coarse jerky tremor of these limbs which persisted and led to his evaluation at Harlem Hospital a year later. At that time he had a normal blood pressure and cardiac status. There was mild flattening of the left nasolabial fold and mild weakness and increased tone of the left limbs, which showed a coarse irregular 5/s tremor with both Parkinsonian and cerebellar features. The rest of his examination and workup were negative. In the ensuing five years, he has taken no heroin or other drugs; his neurological signs have shown no change.

CASE 2

In 1970, a 25 year old heroin addict injected himself intravenously and within an hour noticed weakness which remained for a few days. He was unable to recall if the heroin he gave himself at that time was more than his usual amount, or if it had been his first injection after a period of abstinence.

At the age of 26 years, he began sniffing cocaine and during this period of about two weeks did not take heroin. Then, feeling uncomfortably 'high' on cocaine, he gave himself his usual dose of heroin intravenously and became abruptly unresponsive. Brought to Harlem Hospital, he was comatose with a respiratory rate of 3/min and pinpoint pupils. There was prompt response to nallorphine 10 mg intravenously: respiration increased to 16/min, pupils became mid-position, and he awoke. He was lethargic and had mild difficulty in naming, moderate agraphia (writing with his left hand), alexia, right homonymous hemianopia, right facial weakness, flaccid paralysis of the right arm, and moderate weakness of the right leg. Position sense was decreased in the right fingers, and there were decreased deep tendon reflexes of the right limbs.

White blood cell count was 13 250/ml (70% polymorphonuclears, 27% lymphocytes, 2% monocytes,

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and 1% eosinophils). Haematocrit, platelets, ESR, urinalysis, fasting blood sugar, blood urea nitrogen, serum VDRL and FTA, creatinine, prothrombin time, protein electrophoresis, cerebrospinal fluid, and electrocardiogram were normal. Serum aspartate aminotransferase was 1100 IU/l, and creatine phosphokinase 4900 IU/l. Chest and skull radiographs, electroencephalogram, technetium brain scan, and left carotid arteriogram were normal.

A week after admission after one day's absence from the hospital without permission (but during which he denied further heroin use) he developed chorea of his left arm and leg. Further tests included: ESR 31 mm/h, direct Coombs test positive and indirect negative; serum albumin 28 g/l (42.9% of total), and gamma globulin 17 g/l (42.9% of total) (normal: albumin 58–65% of total, gamma globulin 9.8–14.3%). White blood cell count showed 10% eosinophils. Latex fixation, antinuclear antibodies, LE preparation, repeat cerebrospinal fluid, and several blood cultures were negative, as were technetium brain scan, EEG, and right carotid arteriogram. Haemoglobin electrophoresis showed AS.

Over the next few weeks the chorea improved, and the right arm and leg became spastic. Examined in January 1975, having taken no more drugs, his hemiparesis was unchanged, and his left arm and leg still showed mild chorea.

CASE 3

A 36 year old man with intermittent consumption of heroin for five years was found unconscious on 10 May 1967. He had recently resumed use of intravenous heroin, and injected himself just before losing consciousness (the amount, and whether it was greater than his usual dose, was never clear). Given nallorphine, he failed to awaken and had several major motor seizures with head and eyes turning to the right. Blood pressure was 150/80 mmHg, pulse 100/min and regular, respirations 16/min and regular, and temperature 37°C. Gradually awakening, he showed global aphasia, right facial weakness, flaccid right hemisparesis, and a right extensor plantar response.

Haematocrit was 56%, white blood cell count 17 200/ml (72% polymorphonuclears and 28% lymphocytes). Platelets, urinalysis, blood urea nitrogen, fasting blood sugar, serum VDRL, prothrombin time, and cerebrospinal fluid and chest and skull radiographs were normal. Blood cultures were negative. Technetium brain scan showed increased activity in the anterior left cerebral hemisphere. A left common carotid arteriogram (11 May) showed stenosis of the internal carotid artery at the syphon, with hypervascularity of the lenticulostriate arteries. The anterior cerebral artery was partially occluded proximally, and the middle cerebral artery was totally occluded. The picture did not suggest embolic disease, but rather pathology in the vessel walls themselves. Discharged after eight weeks of gradual improvement, he resumed heroin use and, in October 1967, was found dead in his room. A necropsy by the medical examiner did not include neuropathological observations.

CASE 4

In December 1967, a 38 year old heroin addict took his usual intravenous dose and fell asleep. He awoke after an hour with left hemiplegia and was admitted to another hospital. Records of this hospitalization were lost. He improved minimally over the next several months. Admitted to Harlem Hospital in December 1969, for an unrelated problem, he had spastic left hemiparesis, left hemisensory loss, and left homonymous hemianopia. Blood pressure was 110/60 mmHg. He was still using heroin, but in a lower dose, and had not had symptoms suggestive of additional vascular disease. Last seen in January 1975, he showed no change.

CASE 5

On 15 November 1971, a 38 year old woman, a heavy alcohol drinker and heroin user, was talking with her mother and then fell asleep on a sofa. Her mother left the room and returned a few minutes later to find her daughter 'jumping about and hitting herself'. She then fell to the right and appeared unable to speak. The mother did not know if the patient was taking birth control pills, or if she took drugs other than heroin and alcohol.

Blood pressure on admission was 130/80 mmHg, pulse 60/min and regular, respirations 16/min and regular, and temperature 37.3°C. There were numerous lesions of heroin 'skin popping'. She had global aphasia, right homonymous hemianopia, right facial weakness and hemiparesis, right decreased sensation, and a right extensor plantar response. Haematocrit was 29% and ESR 94 mm/h. White blood cell count, platelets, urinalysis, fasting blood sugar, blood urea nitrogen, and serum VDRL, creatinine, cholesterol, sickle preparation, creatine phosphokinase, and antinuclear antibodies were normal. Prothrombin time was 14.9/11.6 s, and on a serum protein electrophoresis albumin was 33.8% (normal 55–65%), and gamma globulin 44.23% (normal 9.8–14.3%). Latex fixation was positive twice and then became negative after three weeks. Cerebrospinal fluid was normal. Several blood

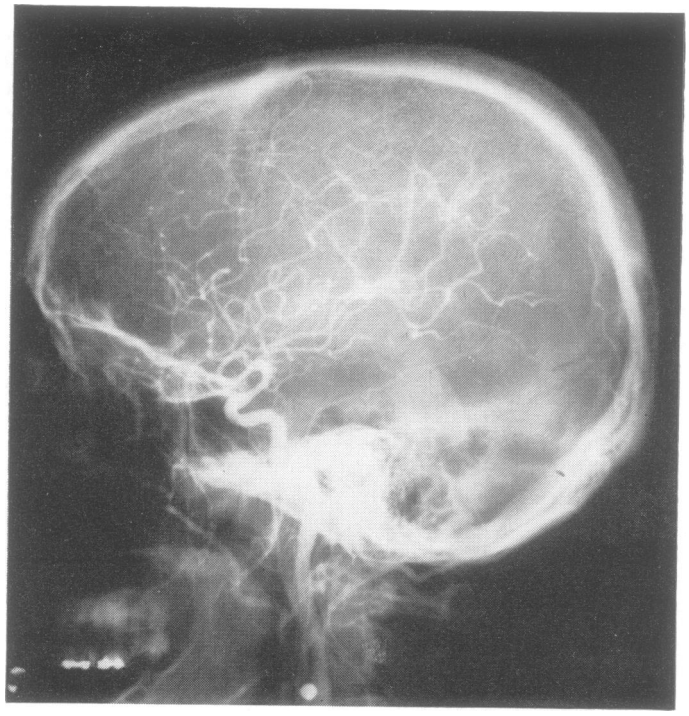

FIGURE *Left carotid arteriogram, case 5, showing scattered segmental narrowings of vessels, suggestive of arteritis.*

cultures were negative; a technetium brain scan two weeks after admission showed a left posterior parietal uptake. EEG and skull radiographs were normal. A left carotid arteriogram showed lesions of small cerebral vessels suggesting arteritis (Figure).

She improved over two weeks and then signed out against medical advice. When last seen in February 1972, aphasia, mild right hemiparesis, and mild right sensory loss were still present.

CASE 6

In 1968 a 28 year old female user of intravenous heroin, not taking oral contraceptives, was admitted after two days of left face and hand weakness, left homonymous hemianopia, and left-sided sensory loss. She had a negative lumbar puncture, EEG showed right slowing, a technetium brain scan showed a right parietal uptake, and a right common carotid arteriogram was normal. In 1970 she was readmitted for left focal motor seizures; she was now taking heroin subcutaneously. Blood pressure was 140/100 mmHg, and pulse 84/min and regular. There was residual left facial weakness, spastic left hemiparesis, and decreased position sense in the left fingers and toes. Cerebrospinal fluid was normal. Signing out against medical advice a week after admission, she has been lost to follow-up.

CASE 7

In 1969 a 42 year old heroin addict showed pedal-oedema, azotaemia, 4+ proteinuria, and hypertension, and a renal biopsy revealed membranous glomerulonephritis. A year later he became suddenly comatose. Blood pressure was 260/100 mmHg, and respirations were of Cheyne-Stokes type. Papilloedema, haemorrhages, and exudates were present in the fundi; pupils were 3 mm diameter and fixed to light; there were no extraocular movements to caloric stimulation, and the limbs exhibited decerebrate posturing to painful stimuli. Cerebrospinal fluid was grossly bloody with xanthochromic supernatant; opening pressure was 600 mm H_2O. He became apnoeic and died the day after admission.

Necropsy, by the medical examiner, revealed massive left intracerebral haemorrhage. The arteries at the base of the brain were considered grossly normal, but smaller cerebral vessels were not commented on, nor was there microscopic evaluation of vessel walls. Morphine was identified in bile and quinine in the brain.

CASE 8

On 21 October 1970, a 45 year old heroin addict was admitted to the Harlem Hospital Methadone Detoxification Unit, where he began receiving methadone 10 mg orally twice daily. His blood pressure was 120/80 mmHg, and his neurological examination was normal. Two days later he had several major motor seizures, and then became comatose with Cheyne-Stokes respirations. Blood pressure was then 120/86 mmHg. Pupils were unreactive to light, and extraocular muscles were unreactive to caloric stimulation. Cerebrospinal fluid was grossly bloody with xanthochromic supernatant and an opening pressure of 450 mm H_2O. He died a few hours later.

Necropsy, by the medical examiner, revealed a massive haemorrhage in the right basal ganglia. The intracranial vessels themselves were not examined.

CASE 9

A 41 year old heroin addict began a methadone maintenance programme in 1970, and six weeks later, having taken no heroin, awoke with right hemiparesis. Blood pressure was 145/100 mmHg, pulse 80/min and regular, respirations 16/min and regular, and temperature 37°C. Moderate weakness of the right face, arm, and leg was present, but there was neither aphasia, a visual field cut, nor sensory loss. Complete blood count, urinalysis, serum VDRL, blood sugar, blood urea nitrogen, cerebrospinal fluid, skull radiographs, EEG, and technetium brain scan were all normal. He improved and was discharged after two weeks with the diagnosis of infarct in the left internal capsule.

DISCUSSION

Many of the neurological complications of heroin addiction were initially recognized at Harlem Hospital Center (Richter *et al.*, 1973; Pearson and Richter, 1975). Aetiological factors are difficult to assess because, typically, the addict obtains an unsterile mixture of heroin adulterated with varying quantities of quinine, lactose, and other diluents. Each packet may contain from 0% to 25% heroin (Baden, 1973).

Of our nine patients, cases 1–4 developed stroke in association with loss of consciousness following intravenous heroin. Cases 5 and 6 were using heroin at the time of the stroke, which, however, was not related to overdose or to a particularly recent injection. Cases 7–9 had strokes of less certain relation to heroin use. Case 7, while still using heroin, had an intracerebral haemorrhage in the presence of glomerulonephritis and severe hypertension. Cases 8 and 9 were taking oral methadone. With case 8, the last heroin had been taken three days before; he was normotensive, yet sustained a massive intracerebral haemorrhage. Case 9 was hypertensive and had been receiving only methadone for six weeks.

There are a number of possible causes of stroke in addicts. Emboli from bacterial or fungal endocarditis are well known (Louria *et al.*, 1967; Cherubin *et al.*, 1968). Hameroff *et al.* (1970) reported focal cerebral involvement by phycomycosis in a non-diabetic addict who at necropsy did not have endocarditis. Addicts with endocarditis were excluded from our series, and none of our patients showed other evidence for an infective cause.

Another possible cause of stroke in heroin addicts is focal ischaemia during a period of shock after overdose and hypoventilation. In the present series, hemiplegia was present in case 2 upon awakening from nallorphine-responsive coma and hypoventilation, and cases 1, 3, and 4 awoke from unconsciousness after intravenous heroin to find themselves hemiparetic; at least one of these three (case 1) had deliberately taken a greater than usual amount of heroin. The facts against so interpreting these strokes are that hypotension was never documented in any of them, the patients did not show the bibrachial palsy of so-called 'watershed infarcts' usually associated with shock, and the patients were young, normotensive, and non-diabetic and therefore unlikely to show the asymetrical atherosclerosis which could lead to unilateral infarcts during hypotension. Moreover, one of these patients showed angiographic changes suggesting large vessel arteritis.

A third possible cause of heroin-related stroke is drug allergy or vessel toxicity. Citron *et al.* (1970) reported 14 patients who used a variety of drugs and who developed an angiitis indistinguishable from periarteritis nodosa. At necropsy one showed infarcts and haemorrhages in cerebrum, cerebellum, and brain-stem. Combinations of heroin and methamphetamine were commonly used, with the latter an apparent common denominator. The authors stressed that the lesions did not resemble hypersensitivity angiitis, which involves smaller arteries, capil-

laries, and venules, implying a direct toxic effect by one or more of the drugs. In a letter commenting on this paper, Gocke and Christian (1970) questioned whether the arteritic lesions could be related to Australia antigen, since they had shown this agent to be present in vessel walls in periarteritis nodosa, and heroin and other addicts would be expected to be exposed frequently to it. Citron and Peters (1971) replied, however, that they had been unable to correlate angiitis with Australia antigen in their cases.

Lignelli and Buchheit (1971) described a 19 year old man who had taken heroin intravenously for a year, plus intermittent LSD, and developed sudden global aphasia. Carotid arteriography showed diffuse cerebral angiitis. Woods and Strewler (1972) reported a 21 year old woman who developed left hemiparesis two weeks after starting daily heroin use and six hours after an intravenous injection. Symptoms were ushered in by vomiting, headache, sweating, and shortness of breath, suggesting anaphylaxis, and arteriography suggested arteritis of the distal internal carotid artery. There was 8% eosinophilia. These features, plus the fact that the heroin she used had been shared at the time by her husband, supported the diagnosis of a hypersensitivity reaction.

Our case 2 had 10% eosinophilia, serum hypergammaglobulinaemia, and a positive direct Coombs test. Case 6 had an ESR of 94 mm/h and two positive latex fixation tests. Cases 3 and 5 had carotid angiography suggesting arteritis. Angiography in case 2, however, was negative.

There are other conceivable mechanisms for stroke in heroin addicts. Quinine, present in most New York City street heroin, has been suggested as a cause of death in some addict fatalities (Levine *et al.*, 1973). A patient has been reported from Harlem Hospital (Brust and Richter, 1971) who developed amblyopia probably secondary to the quinine in his heroin preparation. Other as yet unidentified adulterants may also contribute to strokes, as may emboli from crude contaminants.

Another possibility in our patients is that they did not acknowledge all the drugs they were using. Citron *et al.* (1970) considered methamphetamine the most probable common denominator in their patients with angiitis, and Rumbaugh *et al.*, (1971a, b) have described cerebral arteritis in both humans and monkeys receiving amphetamine. Amphetamine abuse, however, has only rarely been observed among the heroin addicts we have treated in central Harlem. Cocaine abuse, on the other hand, has increased in frequency, and we have recently observed a stroke in a 43 year old man after cocaine injection (Brust and Richter, 1975, to be published). Sobel *et al.* (1971) reported a 14 year old boy who developed left hemiplegia after injecting 4-lysergic acid diethylamide (LSD) capsules; right carotid arteriography showed total obstruction of the internal carotid artery above the syphon.

Case 2 had used cocaine as well as heroin, but his hemiparesis followed an apparent acute reaction to heroin. With case 6 it was never determined if additional drugs were used. The other patients denied using cocaine, amphetamines, barbiturates, LSD, or other agents.

It is not proven, of course, that the strokes in these patients, especially cases 7–9, are more than coincidentally related to their heroin use. The age of cases 1–6, however, ranged from 26 to 38 years (average 33 years), and, with the exception of mild hypertension in case 6, none of them had other predisposing factors, including diabetes mellitus, hyperlipidaemia, blood dyscrasia, oral contraceptive use, migraine, source of emboli, inflammatory disease, or neoplasm to cause a stroke at such a young age. It may well be that, like the question of stroke and oral contraceptives, that of stroke and heroin use will remain unsettled for some time.

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