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"MONDAY HEAD": AN INTERESTING OCCUPATIONAL DISORDER

BY

B. W. McGUINNESS, M.D.

AND

E. L. HARRIS, M.R.C.P., M.R.C.P.Ed.

Nicholas Research Institute, Slough, Bucks

It has been recognized almost since the first introduction of organic nitrates into therapeutics that these compounds are capable of producing headaches.

It is a common experience of the physician that patients with angina pectoris who are under treatment with these compounds have headache as a leading side-effect. However, this is of little importance in practice, partly because habituation occurs readily (Goodman and Gilman, 1955; Laurence and Moulton, 1960) and partly because the therapeutic response producing relief from anginal pain overshadows the discomfort of the side-action.

Industrial workers handling nitrates may absorb sufficient through the surface of the body to produce symptoms, the commonest of which is headache. This, too, has been known for many years, the first description of the effect being published in 1910 (Laws, 1910). Since no therapeutic effect is intended in these cases and since the substance is introduced into the body accidentally, one may legitimately call this an industrial disease referable to chemical toxicity.

There have been many instances of "nitrate head" reported in the literature, the greatest incidence of the condition being just before and during the two world wars, when production of explosives was at its peak. It is indeed interesting to note that the earliest report on nitroglycerin-induced headache is attributed to an Army officer serving during the Boer War (Ebright, 1914). All publications hitherto have understandably dealt with the characteristics, mode of prevention, and treatment of this troublesome disorder produced by nitroglycerin in munition workers, Service men, and miners (Laws, 1910; Ebright, 1914; Rabinowitch, 1944; Schwartz, 1946; Forssman *et al.*, 1958). There have been no accounts of the condition affecting workers using different nitro-compounds in other occupations, and this paper describes, for the first time, nitrate headache in workers in a pharmaceutical manufacturing plant where a new coronary-artery dilator drug was being made.

Basically, the process consisted of the nitration with aqua regia of the dianhydro derivative of sorbitol to produce isosorbide dinitrate, which was then recrystallized from absolute alcohol. After filtration through sintered glass the salt was dried on trays in a vacuum oven at room temperature. When dry the powder was scraped by hand from the trays into glass dishes, in which it was passed to another laboratory for compounding into tablets containing lactose. The final product is a tableted form of the active compound intended for human experimental therapeutics.

The three cases reported below occurred in the development laboratory where the isosorbide dinitrate was in preparation. The manufacturing process was conducted by a team of three men.

Case 1

The subject was a male chemist aged 31 who had always been fit and was not particularly prone to headaches in the ordinary course of events. He was well built and apparently in normal health at the time of starting work in the nitrate plant. He began synthesizing isosorbide dinitrate on the morning of Thursday, April 20, 1961, and continued full-time at the process, working from 9 a.m. to 5.30 p.m., with a break of one hour for lunch, until the afternoon of Saturday, April 22, at 1 p.m.

He was apparently well until 11 a.m. on Saturday morning when he first developed headache, which persisted on that day until 2 p.m. He had no headache on Sunday. On Monday morning, April 24, he started work on the process again and continued full-time each day, being first seen on Thursday, April 27. He gave a history of recurrent headache which reappeared on Tuesday, April 25, and which he experienced every day that he was in the nitrate plant.

The headache occurred about mid-morning and persisted for the rest of the day until he went to bed at night; it dispersed overnight and he felt well each morning until about 11 a.m. Although not severe it caused sufficient discomfort for him to take 5 gr. (0.32 g.) of aspirin. Relief was attained for about 15 minutes on the one occasion that he took the analgesic. The ache was bitemporal in site, it was persistent, and was not throbbing. There was no lancination, and he described it as being "like pressure on each temple." There were no other symptoms at the time; he was not nauseated, nor did he experience tinnitus, vertigo, palpitations, or flushing of the skin.

He always washed his hands thoroughly before meals, did not smoke during working hours, and handled the active compound relatively little. The route of entry of the substance is difficult to trace with certainty; inhalation is a possibility, since the compound is dried from absolute alcohol and it is possible that isosorbide dinitrate dust was present in the atmosphere.

Case 2

A male chemist aged 28 who always enjoyed good health had been employed as an ammunition examiner in the Army between the years of 1951 and 1954, when he was doing his national service in the Middle East. During this employment he had been accustomed to handling guncotton and other explosives in the form of many common varieties of land-service explosives. He experienced headaches during his tour of duty when handling these nitro explosives. He and his fellow Service men called the attacks "N.G. heads," which they regarded as of nuisance value only and which they treated by lying down in a darkened room and drinking cold beer. This method of treatment achieved great repute in the Canal Zone of Egypt.

He began operating in the nitration plant on Wednesday, April 19, at 9 a.m. He first noticed headache on Friday, April 21, during the morning. He recognized the symptom

quite soon as being like "N.G. head." He was well during the two days of the week-end, but there was a recurrence of headache on Monday afternoon, April 24. Since that time he experienced headache each day, the symptoms beginning at about 3 p.m., persisting until he retired to bed at night and recurring about the same time the following day. During week-ends he was asymptomatic; the severity of the headache, while not being great at any time, was more severe during the first week of exposure to nitrate than during the second week.

The site of the discomfort was retro-orbital, bitemporal, and occipital. It was constant in site without radiation and had a dull aching character with occasional lancinating. It was not pulsatile and it was not associated with other symptoms. In particular, no nausea, no vomiting, no visual disturbances, and no auditory symptoms occurred. He was not unduly perturbed by the headache, although he took 10 gr. (0.65 g.) of aspirin on one occasion during the first evening that he had the symptom. This dose of salicylate effectively removed the discomfort for about 15 minutes but did not have any longer-lasting action.

This worker was a qualified organic chemist without any relevant previous medical history, and he always washed well after leaving the nitration plant for meals. He neither smoked nor ate sweets while working. The source of entry of the nitrate in this case is almost certainly by inhalation, since he was not touching the active compound to nearly the same extent as the first subject.

Case 3

A chemist aged 34, this man was always fit and usually free from headaches until he began work on the production of organic nitrate.

He began operations at a later date than the first two subjects and was exposed to the inhalation of nitrate dust, and presumably fumes too, for some hours of his first day in the plant. The day in question was particularly hot and he developed a severe pulsatile headache within three hours of first exposure to the compound. The ache was sited mainly on the top of the head, but there was occipital radiation and some pain in the frontal region. The headache became steadily worse, although he was able to go on working until the end of the day. During the evening it became severe enough to make him anorectic and unable to do more than sit quietly in a chair until it was his usual bedtime. He was unable to sleep properly because of the headache, which gradually diminished during the night and disappeared by the following morning. At its height the headache was associated with a "full" feeling in the head, palpitations, lethargy, and difficulty in mental concentration. The worker did not notice flushing of his skin. During the following day, which was also hot, he again had a very severe headache and complained to those in charge of the plant so that attention was drawn to the condition, thus initiating adequate preventive measures.

With the introduction of exhaust ventilation, the provision of a change of clothing, and the use of shower-bathing at the end of each working period in the nitrate plant, this distressing occupational syndrome did not recur.

Discussion

The syndrome of nitrate-induced headache is characterized by a distressing headache which may be constant and aching but more typically is pulsatile, and which, when severe, is associated with "fullness in the head," palpitations, anorexia, nausea, faintness, tinnitus, mental confusion, flushing of the skin, and, occasionally, visual disturbances (Laws, 1910; Rabinowitch, 1944; Schwartz, 1946). The headache is made worse by stooping and lying down (Rabinowitch, 1944).

The disorder may be encountered in differing degrees of severity, differences between cases probably being

accounted for by degrees of habituation and differences in the amount of nitrate absorbed as well as by differences in individual susceptibility.

There is a constant aetiological association with exposure to nitrate dust and fumes. The speed and power of action of the compound are to a certain extent related to the weather, especially the ambient temperature (Ebright, 1914).

These characteristics are referred to in the several popular synonyms for this interesting condition—for example, "nitrate head," "N.G. head," "powder head," "Monday headache." The last-mentioned term derives from the loss of habituation which occurs during a week-end free from exposure; the other terms have, of course, aetiological significance.

The syndrome is troublesome, although of itself it has little serious prognostic significance for the affected worker (Forssman *et al.*, 1958). However, it is known that alcohol and nitrates are mutually potentiating, and there have been several instances where an individual with nitrate intoxication has gone berserk after taking alcohol (Jennings, 1903; *Brit. med. J.*, 1903; Laws, 1910; Ebright, 1914; Forssman *et al.*, 1958). In a few cases homicide has been committed during the temporary lapse (Ebright, 1914; Hamilton, 1925; Rabinowitch, 1944). For this reason alone the occurrence of the disorder demands the most strenuous efforts on the part of all concerned to eradicate the conditions allowing it to develop.

Workers themselves have discovered that habituation is readily produced (Ebright, 1914; Schwartz, 1946; Modell, 1960), and there have been many cases of men spending 25 years in a nitrate plant, having overcome the initial discomfort associated with exposure (Laws, 1910). These "old hands," realizing the ready loss of habituation that occurs during week-ends away from the plant, are known to rub a little of the nitrate into their hat-bands so that they absorb sufficient when off work to maintain the state of habituation (Schwartz, 1946; Sax, 1951; Goodman and Gilman, 1955).

The alleged aphrodisiac action of nitrates (Laws, 1910) would seem to provide little compensation for the worker with a pounding headache and nausea despite the effect on fertility that these substances are supposed to have (Laws, 1910).

The pathogenesis of the syndrome is referable to the effect of nitrate ions on the arterioles. The headache is probably due to cerebral vasodilatation and a rise in intracranial pressure (Schwartz, 1946; Goodman and Gilman, 1955; Laurence and Moulton, 1960). The mode of entry of the nitrate is either through the skin or by inhalation, or possibly by both routes.

It has been suggested that a psychic factor may be involved in the production of these headaches, since many workers subject to the syndrome realize the danger of handling these explosive substances and may even have witnessed the sudden death or maiming of their colleagues (Schwartz, 1946). However, this is almost certainly a subsidiary and contributing factor to a primarily organic disorder.

The disorder may be prevented by the use of protective clothing, adequate removal of dust and fumes from the workplace (Forssman *et al.*, 1958), and by limiting, so far as is possible, the amount of these produced during milling of the offending material. Prevention is thus a matter of elementary industrial hygiene.

Summary

The occurrence and causation of nitrate-induced headache in industrial workers are reviewed, and three cases occurring in a pharmaceutical manufacturing plant are described. The mode of production of this troublesome syndrome and the ease with which it may be prevented are outlined. The relevant literature is reviewed in the context of the account.

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Medical Memoranda

Pneumatosis Cystoides Intestinalis

Until recently the condition of pneumatosis cystoides intestinalis had rarely been described as involving the large bowel. In only 9 out of 213 cases reviewed by Koss (1952) was the colon the sole site of the disease; the majority involved the small intestine and its peritoneal attachments.

When the large bowel has been implicated, the condition has usually been recognized as the result of symptoms either of dysfunction or of mechanical obstruction of the bowel, directly attributable to the presence of the cysts. This contrasts to the so-called "secondary pneumatosis" of the small intestine related to other pathological processes such as peptic ulceration or neoplasm, which are the prime cause of symptoms. In the large bowel, although previous sigmoidoscopy or minor operative procedure such as polypectomy has been the implied causative factor in the production of the cysts (Marshak *et al.*, 1956), the condition may develop spontaneously. To such cases the term "primary pneumatosis" may accurately be given, and an increasing number of such examples have appeared in recent years in the literature.

The presence of gas cysts affecting the sigmoid colon, and associated with recurrent volvulus of the affected loop, was reported by Jones (1948). Resection was performed in this patient. Witkowski *et al.* (1955) described a case where symptoms of large-bowel obstruction led to the diagnosis, again with resection of the affected portion of bowel as the outcome. A disturbing feature was the later appearance of further cysts in the remain-

ing colon, with no evidence of a tendency to spontaneous remission. Griffiths (1955) reported a case in which pain in the left iliac fossa and passage of mucus and blood per rectum were the presenting symptoms. Diagnosis was made on radiological and sigmoidoscopic findings, and later subacute obstructive symptoms supervened, necessitating resection of the affected bowel. Shoemith and Crone (1959) have treated two further patients in whom the left colon was involved; in one the cystic changes extended into the rectum.

We record below yet another example of severe pneumatosis cystoides intestinalis affecting the left colon and presenting as a volvulus of the involved loop.

CASE REPORT

The patient, a man of 38 and a known severe epileptic, was admitted to hospital on January 18, 1959. He gave a history of severe lower abdominal pain of sudden onset, occurring while he was in bed three hours before admission. He had vomited once, immediately after the onset of the pain, and stated that for the previous three days his motions had been "rather loose."

The past history was difficult to assess as he was of low intellect, being cared for at home by his sister. He had never worked, and epileptiform attacks were frequent despite prolonged and heavy drug treatment. There was no history of dyspepsia or of previous abdominal pain. His sister volunteered the information that he tended to be constipated and had been known to introduce foreign bodies into his rectum.

On admission he was found to be a poor witness, in some pain, but this was apparently much less severe than at the onset. The abdomen was distended, but without rigidity or localized tenderness. Rectal examination showed no evidence of any foreign body or local trauma, and the rectum was empty. His general condition was good, with no evidence of shock. Plain x-ray films of the abdomen in the erect and supine positions demonstrated considerable distension of the large bowel, without the presence of fluid levels. No faecal result was obtained from two enemas.

After admission his pain subsided and it was decided to pursue a conservative regime. There was no further vomiting, and he became less distended, with passage of flatus and some fluid faeces per rectum. Pain recurred, however, and on January 23 a small amount of barium was run into the rectum. This demonstrated an apparent complete obstruction at the recto-sigmoid junction. The barium was retrieved, and sigmoidoscopy demonstrated an impassable obstruction at 20 cm. from the anal margin. It was thought that he had either a recurring volvulus at the recto-sigmoid junction or an impacted foreign body. Laparotomy was performed.

At operation a volvulus of the sigmoid loop through 180 degrees was found to have occurred. The loop of bowel involved was greatly enlarged, but it untwisted readily and was perfectly viable. On examination the affected loop was found to be the site of multiple gas cysts, encroaching on the lumen and projecting on the serosal surface. The rectum and rest of the bowel were quite normal in appearance, there being no evidence of any coincidental lesion in the stomach or intestine. Attempted deflation resulted in very little diminution in the size of the bowel, and the affected portion was resected by the Mikulicz procedure.

HISTOPATHOLOGY

The resected bowel consisted of sigmoid colon, measuring 40 cm. in length, and 13 by 9 cm. in cross-section at its largest part, after fixation. The great increase in diameter was due to the large number of gas-filled cysts situated in the bowel wall, giving the specimen a spongy consistency on palpation.