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The Origins of Analgesic Nephropathy

By ROBIN M. MURRAY

INTRODUCTION

The association between renal papillary necrosis and prolonged ingestion of compound analgesics containing aspirin and phenacetin, has been widely reported (5, 6, 11, 13, 17, 19, 20, 24, 42). Although formerly thought to occur mainly in Switzerland, Scandinavia and Australia, analgesic nephropathy is now being increasingly reported in Britain (3, 26, 36), and in particular in Western Scotland (33). In the past seven years over 100 cases have been seen in the renal unit of the Western Infirmary, Glasgow, and, of these 42 have died in uraemia.

Patients with analgesic nephropathy frequently also suffer from other analgesic-induced disease, including peptic ulceration, gastrointestinal haemorrhage, and anaemia. Indeed, Gault *et al.* (13) believed this to be a 'syndrome of analgesic abuse', which Clarkson and Lawrence (5) described as being 'as remarkable in its consistency and as characteristic as that of the alcoholic but with the same variations and pitfalls'. Many physicians (11, 17, 20, 25, 36) have noted that these patients seldom have an organic reason for taking analgesics, and have commented on the frequency of psychiatric disorder (11, 13, 18-20, 24).

However, in spite of the vast number of reports of analgesic nephropathy (reviewed by 41), there has been little research into its psychological and social origins. This paper reports on such a study.

PATIENTS AND METHODS

The study included all patients with analgesic nephropathy attending the renal unit of the Western Infirmary, Glasgow between 1969 and 1971. For such a diagnosis three conditions had to be met: (i) The ingestion of at least 1 gm. of analgesic daily for three years and the total consumption of a minimum of 3 kg. of aspirin or phenacetin; (ii) The exclusion of any other

cause of renal disease; (iii) Creatinine clearance of 75 ml. per minute or less.

During the three year period 56 patients met these criteria, but 5 were too ill to be interviewed. All but one of the remaining 51 patients were admitted for physical investigation, and all were followed-up by the author at least three-monthly. Over this period a detailed psychological and social history was obtained from these 51 patients, and information regarding demographic details, analgesic habits, medical and psychiatric history, and personal and family history was recorded in a standardized form. Wherever possible relatives were also interviewed and case histories from other hospitals were scrutinized.

For the purposes of analysis of these data the patients were compared with 51 controls who were interviewed in a similar fashion. These were selected from over 300 consecutive medical admissions on the basis that they matched the patients for age and sex (see Table I) and did not take daily analgesics. Any who had been admitted as a direct result of attempted suicide were excluded, and all the controls had organic disease. Where relevant, demographic data were also compared with that of the general population (39).

RESULTS

The ages of the 51 patients ranged from 27 to 72, with a mean \pm standard deviation of 52.2 ± 10.5 years, and females predominated over males in the ratio of 4.1 to 1. Men presented at a significantly older age ($t = 2.32$; $p < 0.0125$) than women (mean ages being 58.9 and 50.6 years, respectively).

Renal papillary necrosis was demonstrated radiologically or histologically in 37 patients, and the clinical picture in the remaining 14 was typical of analgesic-induced renal disease. There were 20 patients with hypertension, and

TABLE I
Comparison of patients and controls

Data	Pa- tients	Con- trols	Statistical significance
Mean age (and range)	52·2 (27-72) yrs.	52·6 (24-71) yrs.	—
Female/male	4·1/1	4·1/1	—
<i>Religion</i>			
Protestant	36	41	} N.S.
Roman Catholic	11	7	
Others	4	3	
<i>Civil status</i>			
Married	30	35	} N.S.
Widowed	8	6	
Single	10	5	
Separated/divorced	3	5	
<i>Class</i>			
I	0	3	} N.S.
II	8	10	
III	25	23	
IV	9	10	
V	9	5	
Left school at minimum age	35	25	p<0·05
<i>Family history of</i>			
Analgesic abuse	22	5	p<0·001
Alcohol abuse	22	4	p<0·001
Psychiatric disorder	20	5	p<0·001
<i>Personal history of</i>			
Parental deprivation (<10)	14	8	N.S.
Gynaecological surgery D. & C.	22	16	N.S.
Previous psychiatric treatment	14	6	p<0·05
Previous attempted suicide	25	5	p<0·001
.. ..	7	1	N.S.
<i>Drugs</i>			
Psychotropic drugs	47	14	p<0·001
Abused alcohol or drugs	10	1	p<0·05
Daily purgatives	15	2	p<0·001
<i>Cigarettes</i>			
None	12	22	p<0·05
<20 per day	13	19	N.S.
>20 per day	26	10	p<0·001

the average creatinine clearance was 26 ml. per minute. Peptic ulcer or gastro-intestinal bleeding had occurred in 19 patients; 9 had

undergone gastric surgery, and 27 were anaemic. These physical features have been described in detail elsewhere (33).

Analgesic habits

The analgesics implicated and their composition are shown in Table II. Forty-five of the patients were taking either Askit powders or compound codeine tablets. Apart from one patient who took simple aspirin, all the rest had taken preparations which contained at least two analgesics (usually aspirin and phenacetin) plus at least one other centrally acting drug (codeine, caffeine or bromide). Women were significantly more likely ($\chi^2 = 4·6$; $p < 0·05$) to take Askit than men (31 out of 41 compared with 4 out of 10).

The intake the patients admitted varied from 2 to more than 15 preparations daily, and the duration of ingestion from 4 to 45 years (average of 6 daily for 20 years). As can be seen in Fig. 1, 31 patients had begun their analgesic consumption before 30 and 16 before 20 years of age. The approximate total dose admitted ranged from 4 kg. of aspirin and 3 kg. of phenacetin to 69 kg. of aspirin and 51 kg. of phenacetin (average of 19 kg. of aspirin and 14 kg. of phenacetin).

Reasons for analgesic ingestion

Twenty-four patients recognized that their main reason for analgesic ingestion was the belief that the drugs had mood-altering properties: 6 believed that they were stimulating, 9 took them for sedation, 4 thought they had both these qualities, and a further 5 were unable to exactly describe their reason. Sedative or stimulating properties were not attributed to any particular preparation.

Twenty-two patients stated that they took the analgesics for headaches. These were usually described as a pressure or fullness and were often precipitated by emotional stress. Some of these patients recognized that the drugs not only relieved their pain but also gave them a feeling of wellbeing. Three patients complained of other pain of a psychogenic nature. Only two had an organic reason for taking the drugs (arthritis), and both of these believed that they also benefited psychologically. In all, 39 patients

TABLE II
Analgesics taken by the patients

	No.	Content of analgesic (mg.)				Other centrally acting constituent
		Aspirin	Phenacetin	Codeine	Phenazone	
Askit powders*	35	550	400	—	—	Caffeine 110 mg.
Compound codeine tablets	10	250	250	8	—	—
Cruikshank's powders† ..	3	—	450	—	120	{ Caffeine 120 mg. Pot. Bromide 1 g.
Beecham's powders*	1	300	210	—	—	Caffeine 20 mg.
Codempirin	1	227	162	8	—	Caffeine 32 mg.
Aspirin	1	300	—	—	—	—

* Phenacetin has been withdrawn from these preparations.

† Production of these powders has stopped at my request.

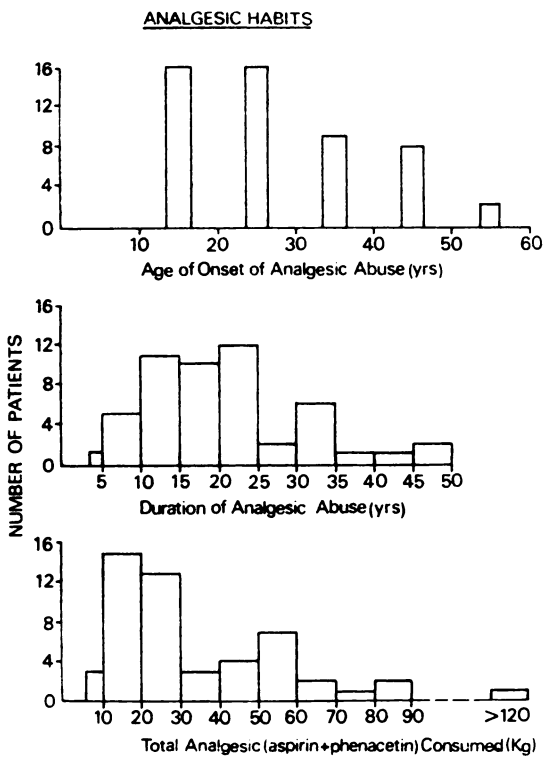


FIG. 1.

believed that their analgesic ingestion had 'become a habit', while 12 maintained that they only took the drugs for pain.

Secrecy and deception

Few patients volunteered information about their drug habits, and 19 strenuously denied

excessive analgesic ingestion. Patients universally minimized the extent and duration of their analgesic intake, and relatives' estimates were often three or four times higher. This reluctance to admit to analgesic ingestion had often led to misdiagnosis:

Case 1

A 58-year-old man presented with renal colic, oliguria, and a blood urea of 200 mg. per 100 ml. He had had a gastrectomy ten years previously and nocturia for several years. Following conservative management he improved, and the blood urea fell to 45 mg. per 100 ml. After discharge he was seen regularly for two years, but the blood urea slowly rose again. He repeatedly denied analgesic ingestion and the diagnosis remained a mystery.

Always neurotic and hypochondriacal, he became severely depressed and was twice admitted to a psychiatric hospital. Only then was his wife asked about his analgesic habits. He had taken 15 or more compound codeine tablets daily since his early twenties to 'buck me up and calm my nerves'. Six months later he died in uraemia and autopsy confirmed papillary necrosis. The next week his wife committed suicide.

Patients had often continued their analgesic habit against considerable family opposition. This was so in 31 of the 38 cases in which a family member was interviewed. Sometimes this objection was merely verbal, but in others the drugs had been hidden by the family. Family opinions ranged from 'it's her only pleasure' to 'she's like a mad thing without a Beecham's'.

None of the patients obtained their drugs on prescription, and they were usually bought in grocers' or corner shops rather than from chemists. In some cases local shopkeepers had refused the patients further drugs, while others

continued supplying the drugs although they realized that the patients were habituated. One chemist, speaking of a customer's use of Cruickshank's powders, stated that when new supplies became available she would be waiting 'shaking like a leaf. We would have to sit her down and give her a powder there and then'.

Persistent analgesic takers

As recovery of renal function depends on abstinence from analgesics (20, 33), patients were strongly advised to abstain. In spite of this, at least 20 continued to take them. Renal function deteriorated in 13, of whom 7 died in uraemia:

Case 2

A 34-year-old woman was referred with polyuria and polydipsia. She was hypertensive and the blood urea was 83 mg. per 100 ml. She admitted taking at least 6 Askit daily for fifteen years. At the age of 19 she had begun abusing drugs from the chemists' where she worked, and at this time many 'bottles of nerve tonics, analgesics and alcohol' had been found in her room. Her personal hygiene then deteriorated, she lost six successive jobs, and sold the family belongings to get drugs. At 21 she was admitted to a psychiatric hospital, where she spent all but seventeen weeks of the next thirteen years. She was diagnosed as having a personality disorder with hysterical traits.

Over the years, in addition to spending much of her hospital allowance on Askit, she abused barbiturates, amphetamines and alcohol, and made five self-poisoning attempts. Even after analgesic nephropathy was diagnosed she was unable to abstain from analgesics, and had six re-admissions with deteriorating renal function following increased analgesic taking. She died in uraemia 33 months after presentation.

Neurological aspects

Unexplained neurological symptoms occurred in 28 patients: 7 had episodes of unconsciousness lasting from a few minutes to two days, 3 had convulsions, 3 were ataxic, and 5 developed toxic-confusional states. A further 5 had salicylate-induced tinnitus or deafness, and 4 had been investigated by neurologists. In the majority these symptoms were due to analgesic intoxication, but in 5 they occurred during analgesic withdrawal. Five other patients had evidence of intellectual impairment. EEG was performed in 25 cases: 10 were normal, 12 showed metabolic encephalopathy, and focal abnormalities were present in three.

Social characteristics

All the patients were Scottish, and their religious persuasion and civil status did not differ from that of the controls or the general population (Table I). Both patients and controls were predominantly from the lower social classes, but significantly more of the patients had ceased their education at the minimum school leaving age ($\chi^2 = 4.05$; $p < 0.05$).

Only 15 patients were working; 21 women had stopped working for normal social reasons, 5 because of psychiatric and 2 because of physical illness. Of the 10 men, 3 had retired, 4 were incapable of working because of psychiatric abnormality and one because of physical illness. None of the patients had a profession. The women had worked mainly as shop assistants, office and factory workers, while the men's occupations simply reflected the local patterns of employment. The totally unskilled were less likely to be working ($\chi^2 = 6.8$; $p < 0.01$).

Family history (includes aunts and uncles)

Patients were much more likely than controls ($\chi^2 = 14.7$; $p < 0.001$) to give a history that another member of the family had abused analgesics. Twenty-two patients gave such a history, and in 6 cases more than one relative was said to have abused the drugs. Of the 29 affected relatives 11 were the mothers and 5 the sisters of the patients, and 11 were known to have analgesic-induced disease.

Patients were also much more likely ($\chi^2 = 16.7$; $p < 0.001$) to volunteer that a relative abused alcohol. This was particularly common amongst the families of women patients, 21 of whom gave such a history compared with only one man ($\chi^2 = 5.6$; $p < 0.05$). In 18 cases the relative's history was suggestive of alcoholism, and in 4 of a severe alcohol problem; fathers and husbands were especially affected.

A family history of psychiatric disorder was obtained from 20 patients but only 5 controls; this difference too is highly significant ($\chi^2 = 11.9$; $p < 0.001$). Although the exact diagnosis could seldom be established, 26 relatives were affected and 4 had committed suicide.

The patients came from large families (mean size = 5.1 children), but sibling rank was not

important. Parental deprivation had occurred in 14 patients as against only 8 controls, but this difference fails to reach statistical significance. A further 4 described their childhoods as unhappy, and 8 had exhibited neurotic traits in childhood. The majority of the women had been poor scholastically.

Marriage

The patients' marital status and age of marriage did not differ from that of the controls or the general population. However, 16 of the 30 married patients believed their marriages were unhappy, and sexual relations were continuing in less than half. Of the 30 married couples 7 were infertile as against only 8 per cent of normals (21). If 5 cases children had required psychiatric treatment.

The women patients had frequently suffered severe dysmenorrhea, and compared with controls significantly more had had dilation and curettage ($\chi^2 = 4.0$; $p < 0.05$)—usually with negative results.

Psychiatric history

Patients were much more likely than controls to have had previous psychiatric treatment ($\chi^2 = 18.8$; $p < 0.001$); 11 had had out-patient and 12 in-patient treatment and 2 were long-term in-patients. As shown in Table III, neurotic and depressive reactions, personality disorder and anxiety states were the main diagnoses that had been ascribed to them. Three had been treated for alcoholism or drug addiction.

TABLE III
Psychiatric diagnosis of the patients

Main diagnosis	Previously assessed	Present assessment
Neurotic or reactive depression	8	7
Chronic neurosis	3	6
Personality disorder	4	5
Presenile dementia	4	1
Anxiety state	2	4
Alcoholism or drug addiction	3	0
Other abnormal reactions ..	1	1
Psychologically normal ..	0	2
	25	26

All but five of the remainder had attended their own doctors for nervous disorder, and only two were psychologically normal. Again, neuroses and personality disorder of an inadequate nature were the rule. Two thirds had chronic insomnia, and seven had previously attempted suicide. There was no relation between the severity of physical disease and psychiatric morbidity.

Psychotropic drugs had been taken in the previous three years by 47 of the patients compared with only 14 of the controls; this difference is highly significant ($\chi^2 = 41$; $p < 0.001$). The majority had been taking hypnotics, but 35 had also received tranquillizers and 12 antidepressants. Six patients had abused tranquillizers, 4 alcohol, 2 amphetamines, and 2 opiates.

Daily purgative taking was much more common amongst the patients than controls ($\chi^2 = 11.9$; $p < 0.001$), and was particularly common amongst those taking Compound Codeine tablets (5 out of 10). Patients not only smoked more frequently than controls ($\chi^2 = 5.2$; $p < 0.05$), but were also more prone to smoke more than 20 cigarettes a day ($\chi^2 = 10.9$; $p < 0.001$).

DISCUSSION

This study confirms that patients with analgesic nephropathy take analgesics for inappropriate reasons. Drug abuse is defined (49) as 'the consumption of a drug apart from medical need or in unnecessary quantities', and clearly my patients' use of analgesics falls into this category. These patients seldom volunteered information about their drug habits, and in many cases persistently denied analgesic abuse. Assessment of analgesic consumption therefore required an oblique approach via headaches or other symptoms, and frequently further evidence had to be sought from relatives. Furthermore, for at least 20 of the patients knowledge of the consequences of analgesic abuse was no deterrent to continued consumption.

Thus these patients exhibited many of the features of drug dependence, and indeed several physicians have remarked that they believed their patients were habituated or addicted (2, 5, 11, 18, 20, 29). Although the W.H.O. Expert

Committee (48) did not consider the possibility of dependence on minor analgesics, Wilson (44) has described this and has suggested that it is associated with psychic dependence, psychotoxicity and possibly tolerance.

My patients undoubtedly showed psychic dependence in that they had 'a psychic drive for continuous . . . administration of the drug' (47). Most had begun taking the analgesic for pain, but the dependence resulted from appreciation of effects other than the analgesic action. The amounts of caffeine which the patients were taking would have a marked stimulating effect (8, 16, 46), and Driesbach and Pfeiffer (8) have shown that the caffeine withdrawal headache, by causing further analgesic consumption, provides 'a plausible explanation for the hitherto empirical addition of caffeine to many headache mixtures'. In addition, phenacetin has mild anxiolytic properties (9, 37, 46) and many people find it pleasurable (37), while the dependence-producing qualities of both codeine (10) and bromide (16) are well known. Thus, the patients' dependence can be largely attributed to the psychoactivity of the analgesic mixtures, in which the psychotropic effects of the constituents are potentiated (27, 28, 46). Nevertheless, one must also consider the role of the extensive advertising of proprietary analgesics for neurotic complaints in reinforcing the dependence.

There was, too, a tendency to increase the dose taken, which was augmented by symptoms of analgesic intoxication, caffeine withdrawal and eventually uraemia. Thus the drugs were taken for symptoms which they themselves had caused, and a vicious circle of decreasing health and increasing intake of analgesics was set up. Although a specific withdrawal syndrome has been described previously (23, 40, 43) and although bizarre neurological manifestations were common, only in a minority could these be ascribed to drug withdrawal.

Women are more prone both to use (22, 34) and to abuse analgesics (1, 38), and consequently women have predominated in every series of analgesic nephropathy except one (17). Analgesic taking is commoner in the lower social classes (34), and in my patients may also have been related to their low intelligence and poor

education. Although Swiss workers (2, 23) have suggested that analgesic abuse in women is often a response to the strain of both working and raising a family, only six of my patients were doing this. Work was not a major source of stress, but it was of some interest that a third of the women had had access to analgesics at their place of employment.

Several authors (12, 17) have noted the familial occurrence of analgesic nephropathy. That 43 per cent of my patients had a relative who also abused analgesics suggests that the disorder stems from abnormal attitudes to analgesics which are often family transmitted, particularly by mothers introducing their children to excessive analgesic taking. The close family association of analgesic abuse and alcoholism is of interest in view of the suggestions of Whitlock *et al.* (45) that the incidence of alcoholism and drug abuse in a community complement each other, and that female drug dependence is the equivalent of alcoholism in the male. Certainly alcoholism is very common in Glasgow, and there is a similar high incidence in the families of patients who attempt suicide with drugs (35).

The patients had often suffered parental deprivation or unhappy childhoods, and although they did not have the high divorce rate which others have noted (5, 15, 20) over half were unhappily married. Sexual difficulties and heavy drinking by husbands were major causes of marital discord. Amongst single women, two thirds of whom were socially isolated, loneliness was an important factor. Stressful events were often important in starting and perpetuating analgesic abuse.

The majority of my patients showed evidence of either personality disorder of an inadequate nature or proneness to neurotic breakdown. To my knowledge, there has been only one previous study of psychosocial factors in analgesic nephropathy (18), but many physicians have commented on the frequency of psychiatric disorder in their patients (11, 19, 20, 24, 25). In particular, Gault *et al.* (13) noted 'emotional instability of an immature and dependent nature', while Gsell *et al.* (19) believed that 'a depressive syndrome and temperamental instability were the most common expressions', and

Whitlock *et al.* (45) concluded that analgesic abusers often 'showed features of personality disorder'. Furthermore, although psychiatric patients are especially prone to abuse analgesics, abuse is rare amongst those with functional psychoses (1, 31).

My patients' frequent previous hospital attendances and their unnecessary gynaecological investigations were a reflection of their hypochondriacal and pain-prone personalities, and their tendency, possibly because of limited intelligence, to somatize emotional conflict. Because of the frequency of attempted suicide, there have been suggestions (23) that patients with analgesic nephropathy wish to harm themselves. This seems unlikely, as before their initial presentation they were seldom aware of the dangers of analgesic abuse. The frequency of alcoholism (11, 14, 18, 19), abuse of other drugs (11, 19, 24, 25), and excessive smoking (5, 11, 24) has been previously noted; in addition, my patients often abused purgatives. There can therefore be little doubt that they were dependence-prone.

Thus analgesic nephropathy in Western Scotland is psychosocial in origin. Those who become dependent on analgesics are vulnerable because of their inadequacy and disturbed background. Indeed, those with least psychological and social resources are most likely to continue analgesic abuse against medical advice (32). Like alcoholics with cirrhosis, patients with analgesic nephropathy are merely the tip of an iceberg of analgesic abusers. Further studies are needed to assess the extent of analgesic dependence in the community.

SUMMARY

Analgesic abuse is a common cause of renal failure in Western Scotland. The mean age of 51 such patients studied was 52.2 years, and women outnumbered men 4.1 to 1. Askit and Compound Codeine Tablets were the main preparations abused, and the average amount taken was 6 preparations daily for 20 years. The cause of the abuse was dependence on the psychotropic effects of caffeine, phenacetin, codeine and more rarely bromine.

When compared with matched controls, the patients were more likely to have a family

history of analgesic abuse, alcoholism and psychiatric disorder. Almost all showed evidence of personality disorder or neurosis, and 25 had had previous psychiatric treatment. They were also prone to abuse other drugs, to take daily purgatives and to smoke excessively.

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