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Analgesic Nephropathy: Clinical Syndrome and Prognosis

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Summary

Over a five-year period 86 patients presented to a renal unit with a history of prolonged analgesic abuse and no other obvious cause of renal damage. Anaemia and peptic ulceration were common, and neurological states suggestive of chronic analgesic intoxication occurred in 22 patients. Thirty-two patients died during follow-up, but the prognosis was much better in patients who ceased abuse of compound analgesics, and improvement could occur even in advanced renal failure. While 84 patients had taken mixtures containing both aspirin and phenacetin, papillary necrosis was also found in two patients who had abused only aspirin, and when phenacetin was withdrawn from several leading compound analgesics, renal function continued to deteriorate in patients ingesting those preparations.

Introduction

Though the association between analgesic abuse and renal impairment has often been recorded (Spuhler and Zollinger, 1953; Nordenfelt and Ringertz, 1961; Rapoport *et al.*, 1962; Harvald, 1963; Dawborn *et al.*, 1966; Prescott, 1966; Gault *et al.*, 1968; McMillan *et al.*, 1968; Fellner and Tuttle, 1969), there have been few reports on the long-term prognosis of such patients. The present report concerns our clinical experience of the syndrome and the outcome of prolonged follow-up.

Patients and Methods

The study included all patients presenting to a renal unit in the period 1965–9 with a history of ingestion of more than 1 kg of phenacetin or aspirin and no other obvious cause of renal damage. Estimation was made of the patients' blood urea and electrolytes, creatinine clearance, urine cell and bacterial counts, plus full haematological examination and intravenous pyelography. Where indicated, isotope renogram, barium meal, and electroencephalography were performed.

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All patients were initially acquainted with the dangers of continued analgesic abuse and advised either to abstain from analgesics completely or to substitute small doses of paracetamol for their previous analgesic. Thereafter they were repeatedly questioned regarding their analgesic habits at regular outpatient appointments, and all those still attending were admitted to the unit early in 1970 for reassessment.

Findings

Clinical Features.—A total of 86 patients were seen over the period of the study. Their ages ranged from 27 to 72, with a mean of 53 years. Females predominated over males in the ratio 5·1:1. The analgesics implicated are shown in Table I. In only two cases did the analgesic not contain both phenacetin and aspirin. The daily intake varied from 2 to more than 15 preparations daily and the duration of abuse from 3 to 45 years (average of five daily for 16 years). The approximate total dose ingested ranged from 2 kg of phenacetin plus 2 kg of aspirin to 51 kg of phenacetin plus 69 kg of aspirin (average 13 kg of phenacetin plus 17 kg of aspirin). Only six patients took analgesics for pain of an obviously organic nature. Fifty-six took analgesics for headache of a psychogenic type, four for other psychogenic pain, and 20 for what they believed were their psychopharmacological effects.

TABLE I—*Analgesics Taken by Patients*

Analgesic	No. of Patients	Content of Analgesic (mg)		
		Aspirin	Phenacetin	Codeine
Askit Powders*.. ..	59	550	400	—
Tab. codeine co. ..	12	250	250	8
Beecham's powders* ..	6	300	210	—
Aspirin	2	300	—	—
Others	7	+	+	—

*Phenacetin has been withdrawn from these preparations.

Gastrointestinal Features.—Dyspeptic symptoms were very common; alimentary bleeding had occurred in 16 patients, radiological evidence of peptic ulceration was obtained in 24, and 14 had undergone gastric surgery.

Haematological Features.—Seventy-four patients had haemoglobin levels of less than 80% (11·8 g/100 ml). In 40 this appeared to be due to diminished renal function, while frank haemolysis was found in 14 patients with seven having sulphaemoglobinaemia or methaemoglobinaemia. Iron deficiency and gastrointestinal bleeding accounted for anaemia in a further 16 patients, while one had a sideroblastic anaemia and three a macrocytic blood picture.

Renal Function.—Patients were divided into two groups on the basis of their blood urea.

Group A.—In 16 patients the blood urea was within the normal range for our laboratory of 0-40 mg/100 ml. The mean creatinine clearance ± standard error for 13 of these patients was 67 ± 7 ml/minute. Eleven patients had increased urinary white cell excretion and eight bacteriuria, while hypertension (diastolic > 110 mm Hg) was present in three.

Group B.—The blood urea was raised in 70 patients. Creatinine clearance was carried out in all but seven, the mean ± standard error being 16 ± 2 ml/minute. Twenty-nine had sterile pyuria, 22 pyuria plus bacteriuria, and three bacteriuria alone. Thirty patients had hypertension (diastolic ⩾ 110 mm Hg) at some point in the illness.

Intravenous pyelography was performed in 63 of the 86 patients. In only nine cases was this normal, and in seven of these the creatinine clearance was greater than 50 ml/minute. Reduction in renal size was the commonest abnormality, while caliceal deformities were present in 13. Calcification or calculi occurred in 10 and hydronephrosis in three. Renal function was so poor in 10 patients that renal outlines could not be distinguished even with infusion pyelography. In most cases the appearances could not be convincingly differentiated from those of chronic pyelonephritis. Isotope renography was performed in 31 patients, but the appearances were not of diagnostic value. On the other hand, sterile pyuria, renal colic, and haematuria were important diagnostic features and occurred in more than one-quarter of the patients, presumably during an episode of acute papillary necrosis.

Psychological and Neurological Features.—Information regarding psychological or neurological symptoms was available for only 60 of the patients. Twenty-six of these had required previous psychiatric treatment and a further 19 were thought to be suffering from unrecognized psychiatric disorder. Unexplained neurological symptoms occurred in 22 patients. Six had episodes of unconsciousness lasting from 30 minutes to 2 days, four had convulsions, three tinnitus and deafness, two visual hallucinations, and five evidence of dementia. Transient neurological signs were common and in four patients cerebral neoplasm had been suspected, resulting in investigation to the extent of ventriculography and angiography. Electroencephalography had been performed in 23 patients, in only three of whom was the blood urea greater than 100 mg/100 ml. Nine were normal, eight showed diffuse abnormalities suggestive of metabolic encephalopathy, while focal abnormalities were present in six.

Outcome

DIED WITHOUT RECOVERY

Five patients died within one month of their initial presentation. Three of these had greatly increased their analgesic consumption on feeling ill—a mechanism responsible for sudden deterioration in several other patients in the series. All five had presented in advanced renal failure; massive renal infection was the immediate cause of death in one, intracranial haemorrhage in two, and the remaining two died of renal failure.

IN RELATION TO SUBSEQUENT ANALGESIC HABITS

Group A.—Of the 16 patients with normal blood urea 11 were discharged symptomless between three months and three years later. Three others ceased abuse but continued follow-up because of persistent pathology (hypertension in two and recurrent urinary tract infection in one), and two continued abuse but declined further supervision.

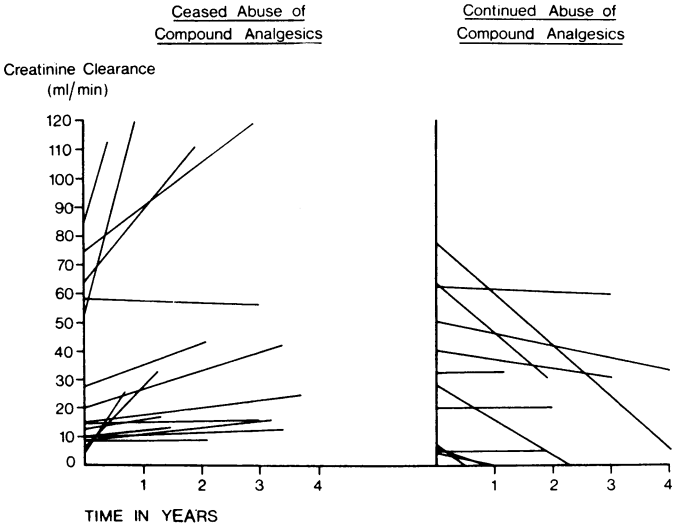
Group B.—The 65 patients with raised blood urea who survived the initial month were followed up for periods ranging from 2 to 120 (mean 29) months:

Aspirin Abusers.—Both these patients continued their abuse and died of renal failure (mean survival 40 months).

Abusers of Compound Preparations Containing Phenacetin.—These patients were divided into three groups: (1) 26, ceased abuse of compound preparations, (2) 28 continued abuse of compound preparations, and (3) in 9 subsequent analgesic habits were doubtful. The outcome among these patients is shown in Table II. The prognosis was much better for those who ceased abuse of compound preparations containing phenacetin. Of the 26 who ceased abuse three died of renal failure (mean survival 63 months) while renal function remained static in six and was improved in 17. On the other hand, of the 28 patients who persisted in abuse renal function deteriorated in 23, of whom 11 died of renal failure (mean survival 24 months), and remained static in the other five. The deterioration in renal function in the two groups was significantly different ($\chi^2=10{\cdot}17$; $P<0{\cdot}005$). These trends are shown in the Chart which gives sequential creatinine clearances where available. No difference in prognosis could be found between those who abstained from analgesics entirely and those who took small doses of paracetamol or aspirin when necessary. In patients who persisted in abuse of compound preparations deterioration in renal function continued when the manufacturers withdrew phenacetin from several of the most popular preparations.

TABLE II—*Outcome of Follow-Up*

	No. of Patients	Renal Function			Died of Chronic Renal Failure	Died of Other Cause	
		Improved	Static	Decreased		With Renal Function Decreased	With Renal Function not Decreased
Ceased abuse of compound analgesics ..	26	16	5	0	3	0	2
Continued abuse of compound analgesics ..	28	0	5	10	11	2	0
Continued abuse of aspirin ..	2	0	0	0	2	0	0
Subsequent analgesic habits doubtful ..	9	1	0	1	5	2	1



Renal function in relation to subsequent analgesic habits.

IN RELATION TO URINARY TRACT INFECTION

Patients in whom urinary tract infection was not a problem had the best prognosis. Persistent infection was associated with deteriorating renal function. Since this usually occurred in patients who were continuing analgesic abuse, however, it was difficult to ascertain the role of infection in the deterioration. There is no doubt that acute pyelonephritis was a serious hazard and the immediate cause of death in at least five patients.

IN RELATION TO OTHER FACTORS

Age and sex were not directly related to prognosis, and neither hypertension nor proteinuria was of prognostic value.

MORTALITY AND PATHOLOGICAL FINDINGS

Over the period of the study 32 patients died. Uraemia was the major cause of death in 25. Five died from vascular causes associated with hypertension, one from gastric haemorrhage, and one from bronchial carcinoma.

Necropsies were performed in 20 cases. In 17 the classical findings of papillary necrosis (acute or previous), chronic interstitial nephritis, or excess lipofuscin were found. In view of the circumstantial evidence (*British Medical Journal*, 1969) of a link between analgesic abuse and renal pelvic tumours, it was notable that these did not occur in any patient. Neuropathological specimens were examined in seven patients. In four of the five phenacetin abusers there was evidence of increased neurofibrillary change and senile plaques, while no such abnormalities were detected in the two aspirin abusers. These findings will be reported in detail elsewhere.

Discussion

The association between analgesic abuse and renal impairment has often been reported and the syndrome has been extensively reviewed (Shelley, 1967; Kincaid-Smith, 1968; Levin, 1969; *British Medical Journal*, 1970). The predominance of middle-aged women with psychiatric disorders has been previously noted (Dawborn *et al.*, 1966; McMillan *et al.*, 1968), as has the high incidence of peptic ulceration and anaemia (Prescott, 1966; Dawborn *et al.*, 1966). Our results confirm the diagnostic value of sterile pyuria (Bell *et al.*, 1969) and renal colic and haematuria (Dawborn *et al.*, 1966), as these occurred in more than one-quarter of our patients. Urinary tract infection was not uncommon, particularly in the terminal stages, but appears less common than in Sweden, where Bengtsson and Hood (1965) found 60% of cases of chronic non-obstructive pyelonephritis to be associated with analgesic abuse. Nevertheless, in contrast to previous workers (Lindvall, 1960; Fairley and Kincaid-Smith, 1968), we could not convincingly distinguish the radiological appearances from those of chronic pyelonephritis.

The frequency of neurological symptoms, in the absence of gross uraemia, in analgesic nephropathy has not been previously noted, but Greer *et al.* (1965) described similar states with hallucinations, tinnitus and deafness, confusion, and transient neurological signs in cases of "chronic salicylate intoxication." Kasanen and Valleala (1963) reported similar E.E.G. changes of metabolic encephalopathy in phenacetin abusers but not focal abnormalities, and like them we found that the changes usually resolved after withdrawal of analgesics. Chronic analgesic intoxication was confirmed in several patients who had high serum salicylate levels, and patients and their families often commented on the pronounced improvement in personality which occurred after analgesic withdrawal.

Our experience of these patients, in keeping with that of Young *et al.* (1965) and of Maisel and Priest (1964), has been that not only do they seldom volunteer information regarding their drug habits but in many cases they will strenuously deny analgesic abuse. This often led to misdiagnosis. Patients had commonly been investigated for chronic anaemia and chronic pyelonephritis and, more rarely, for cerebral neoplasm; others had been operated on for recurrent peptic ulceration, fitted with hearing aids, or treated for other drug addiction. Seldom, however, had the history of analgesic ingestion been elicited; its causative role had not been appreciated and renal function had continued to deteriorate.

There remains considerable doubt regarding which constituent of analgesic mixtures causes the renal damage. The major ingredients—aspirin, phenacetin, and paracetamol—have all been shown to be potentially nephrotoxic (Harvald, 1963; Clausen, 1964; Prescott, 1966, 1969), and though phenacetin has been most often blamed, recent animal work has suggested that aspirin is the major cause of experimentally induced papillary necrosis (Nanra and Kincaid-Smith, 1970). That this may be true in the clinical situation is suggested by the fact that two patients who abused only aspirin were shown to have papillary necrosis at necropsy and that when phenacetin was withdrawn from several of the most popular preparations of abuse renal function continued to deteriorate in patients ingesting them.

There was no doubt, however, that the critical therapeutic measure for most of the patients was to achieve withdrawal of the compound analgesic. Renal function continued to deteriorate in 23 of the 28 patients who persisted in abuse, but in only 3 of the 26 who ceased, two of whom had ineradicable urinary tract infection, while the third after initially requiring acute haemodialysis recovered sufficient renal function to live for 10 years. Of the 26 patients who ceased abuse, renal function remained static in 6 and improved in 17. This did not appear to be influenced by whether they abstained from analgesics entirely or took small amounts of paracetamol or aspirin when necessary. Improvement occurred both in those with considerable remaining renal function and in those with a creatinine clearance of less than 10 ml/minute. Other workers have reported similar improvement in smaller numbers of patients (Harvald, 1963; Bell *et al.*, 1969), and, like Bell *et al.* (1969), we have found pyelonephritis to be the maior hazard.

We therefore conclude that analgesic nephropathy is a relatively common cause of chronic renal failure in Western Scotland. The diagnosis should always be considered in patients with the clinical syndrome even in the face of denial of abuse by the patient, and further evidence should be sought from the patient's family. Considerable effort should be made to achieve and maintain analgesic withdrawal, since noticeable improvement is possible even in advanced renal failure. Because of this potential for recovery these patients merit energetic treatment, including dialysis if necessary, in the period immediately after presentation, and both at this time and thereafter pyelonephritis is the major complication to be avoided.

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Septic Gonococcal Dermatitis

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Summary

The overall incidence in gonorrhoea of septic gonococcal dermatitis was found to be 1·9% (3% for the females and 0·7% for the males). In 23 patients the common presenting symptoms were arthritis or arthralgia and bouts of fever, but the characteristic skin lesions served as an early clue to the diagnosis, and *Neisseria gonorrhoeae* was isolated from the genitourinary tract or from the blood. With the use of immunofluorescent techniques gonococci were also found in smears prepared from the skin lesions. An immune response to gonococci was found with the complement fixation technique in 90% of the patients. The response to treatment with penicillin was prompt, with complete relief from joint pains and fever, usually within two to seven days. The skin lesions faded within a few days, but scars could be observed for up to four weeks.

Introduction

Skin lesions and arthritis in gonorrhoea were described as early as 1893 by Vidal. The syndrome of fever, arthritis, and cutaneous manifestations in association with gonococcaemia was noted by Silvestrini (1903). Several reports of this syndrome appeared in the pre-antibiotic era and two clinical forms were distinguished—one relatively benign, the other fulminant with fatal endocarditis (Cohn, 1936; Levin and Silvers, 1937; Lichterman, 1937; Keil, 1938; Reitzel and Kohl, 1938).

After the advent of penicillin there were no reports of this type of complication of gonorrhoea until that of Abu-Nassar *et al.* (1963). Since then several authors have drawn attention to this syndrome (Kvorning, 1963; O'Sullivan, 1964; Ackerman *et al.*, 1965; Fred *et al.*, 1965; Björnberg and Gisslén, 1966; Danielsson and Michaëlsson, 1966; Wolff *et al.*, 1970). Septic gonococcal dermatitis is a more relevant name, since it has been shown with cultural methods and fluorescent antibody techniques that the cutaneous manifestations are due to the embolization of gonococci with a genitourinary gonorrhoea as the primary focus (Kahn and Danielsson, 1969).

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Most patients with septic gonococcal dermatitis have no symptoms indicating a venereal disease (Abu-Nassar *et al.*, 1963; Kvorning, 1963; O'Sullivan, 1964; Ackerman *et al.*, 1965), and it is certain that some are treated with penicillin or other antibiotics without a specific diagnosis but with prompt therapeutic response. It is also the experience of many authors that some patients recover without treatment. This type of complication of gonorrhoea is therefore easily overlooked, resulting in difficulties in getting information regarding its frequency and epidemiology.

Patients and Methods

PATIENTS AND PERIOD OF STUDY

Our attention was drawn to septic gonococcal dermatitis at the hospital in Örebro City in November 1968 when *Neisseria gonorrhoeae* was isolated from the blood of a man with fever, septic skin lesions, and minor joint affections. Since then 22 further patients with this disease have been seen at our hospital during a 20-month period. The monthly distribution of the cases is shown in Fig. 1. A presumptive diagnosis of septic gonococcal dermatitis was considered in patients presenting a history of moderate discomfort, with or without joint affections and bouts of fever, and with typical skin lesions similar to those described and excellently illustrated with colour prints by Abu-Nassar *et al.* (1963) and Ackerman *et al.* (1965). The diagnosis was considered to be conclusive when gonococci were found in skin lesions or isolated from the genitourinary tract or from the blood according to techniques described below. In one patient the diagnosis was based on the presence of skin lesions, arthritis, a high serum titre of gonococcal antibodies, and a prompt therapeutic response to penicillin therapy.

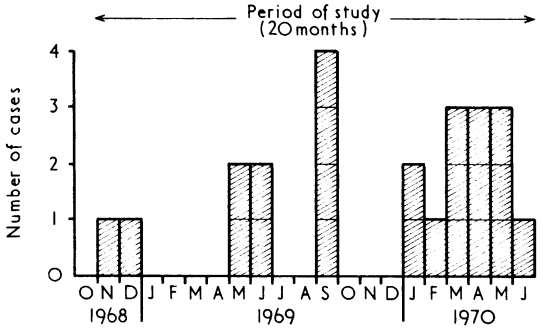

FIG. 1—Monthly distribution of patients with septic gonococcal dermatitis during a 20-month period.