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Analgesic Habits of 500 Veterans: Incidence and Complications of Abuse

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CONSIDERING the number of drugs available legally without prescription, the extent of habituation to analgesics may be exceeded only by that of habituation to nicotine and alcohol in many areas, including North America, Australia and numerous European countries. Consumption of analgesics in general, and phenacetin in particular, has increased in many areas at rates far exceeding population growth, having doubled within a recent 10-year period in the United States, Canada, Australia, Denmark and Switzerland.[1-4]

There is evidence from a vast literature that serious complications, which may include anemia, peptic ulcer, upper gastrointestinal bleeding and renal disease, are common in those who abuse mixed analgesics containing phenacetin, most often in association with acetylsalicylic acid (ASA) and caffeine. Many who do so seem unaware of the associated dangers.

To provide information about the analgesic habits of hospitalized Canadians, we have studied the incidence of abuse, associated predisposing factors and complications in 500 veterans.

Evaluation of Analgesic Consumption

Five hundred consecutive patients who were admitted to Queen Mary Veterans' Hospital during the autumn of 1966 were interviewed and their records examined by one or more of the authors in relation to analgesic consumption. Twelve were females. Emphasis was placed on determining the reason for use of analgesics, and the type, duration, frequency and amount of consumption. Some patients denied use of analgesics before being confronted with the fact that a positive urine ferric chloride test* demonstrated the presence of salicylates. Study of medical records (often from several admissions and visits to the outpatient department) and further questioning permitted a decision as to whether the patient had consumed a significant quantity. In doubtful cases, family members were questioned where possible.

Analysis of 183 Patients Who Frequently Took ASA or Mixed Analgesics

Of the 500 patients (Fig. 1), 110 admitted taking analgesic tablets containing acetylsalicylic acid (ASA) 220 mg., phenacetin 160 mg., caffeine citrate 32 mg. and in almost all cases codeine phosphate 8 mg. (APC and C); 73 took ASA alone. All 183 patients took analgesics at least three times a week with a minimal average daily intake of one tablet for at least one year. The average number of mixed analgesic tablets taken per day and the total estimated consumption of phenacetin are shown in Fig. 2. The chief reasons given for consumption in 183 cases were headache in 68% and arthritis in 16%. Thirty-two patients were considered to take analgesics in excessive quantities.

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*Performed routinely on this group of patients using Phenistix, supplied in part by Ames Co. of Canada Ltd., Toronto, Ontario.

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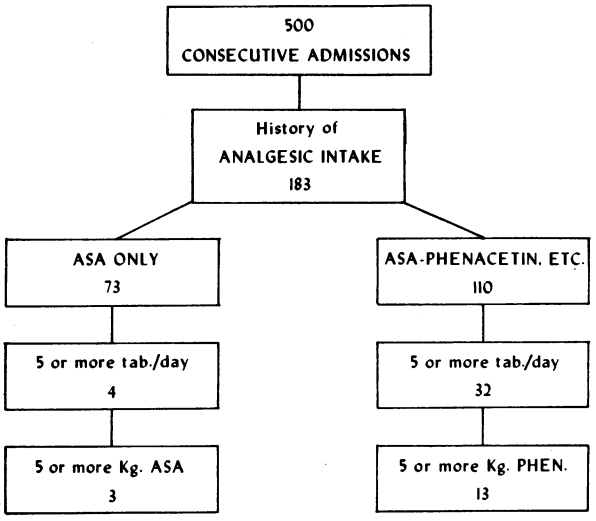

Fig. 1.—Analgesic habits of 500 consecutive patients admitted to the Queen Mary Veterans' Hospital, 1966. Mixed analgesic tablets usually contained ASA 220 mg., phenacetin 160 mg., caffeine citrate 32 mg. and codeine phosphate 8 mg. ASA tablets were almost always 5 grains.

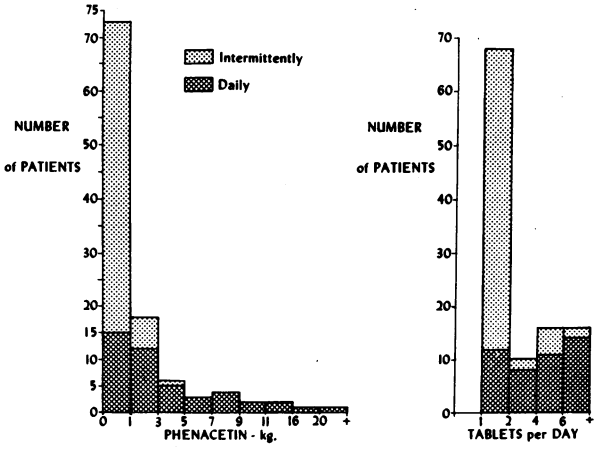

Fig. 2.—(a) Estimated total phenacetin ingested and (b) number of tablets taken daily by 110 patients who took mixed analgesics. ASA ingestion approximates 1.4 times the amount of phenacetin consumed.

Analysis of 32 Patients Who Abused Analgesics

Criteria for analgesic abuse or excessive use were defined as the consumption of an average of at least five tablets per day over a minimal period of three years, with a total consumption of ASA or phenacetin of at least 1 kg. Other authors have defined abuse in relation to phenacetin as the daily ingestion of 0.9 to 1 g. daily for one to three years.[5-8]

All 32 patients were males; ages ranged from 44 to 79 years, with an average of 52 years. Twenty-five took analgesics daily and seven intermittently. Twenty-eight patients used APC and C type analgesics; their approximate average intake of phenacetin was 6 kg., of ASA 8 kg., of caffeine 1 kg. and of codeine 0.3 kg., for an average duration of nine years. Daily intake ranged from 5 to 20 tablets. Four patients consumed ASA only, having taken a total of 4, 10, 15 and 20 kg. respectively over a period of 15 to 20 years.

Chief Reason for Analgesic Consumption

Eighteen patients stated that the chief reason for taking analgesics was headache, often said to be migraine but seldom typical of this disorder. In seven the main cause given was arthritis, in three it was low back pain and in four it was chronic epigastric distress. A few patients who apparently took APC and C primarily for a somatic complaint also received a psychological lift from this combination. One patient with headaches also frequently put APC and C tablets in alcoholic beverages to obtain a "cheap drunk".

Associated Medical Disorders

Twelve patients had a diastolic blood pressure of at least 100 mm. Hg recorded at some time; in eight of these it averaged 100 to 110 mm. Hg without treatment. Three patients were believed to have passed renal calculi and one had recently had a prostatectomy. Cirrhosis of the liver was known to be present in two patients, of whom one was in an advanced phase. One patient suffered from carcinoma of the stomach with metastases, one from long-standing diabetes, one from paraplegia and one from occlusive arterial disease.

Psychiatric Disorders and Alcoholism

Eighteen patients had been treated in a psychiatric ward and four patients had been seen by a psychiatrist in consultation. The chief psychiatric diagnoses listed were depressive reaction in 13 and chronic anxiety in six; two were considered to have "schizoid" personalities and one hysteria. Ten of the 22 and three others were considered to be chronic alcoholics; each had had two or more admissions precipitated by acute intoxication. Marital disharmony, unsatisfactory work adjustment, abuse or misuse of other drugs and long-standing personality disorders were frequently observed.

Gastrointestinal Disorders

Twenty-six patients had a history of gastrointestinal disorder (Table I). In 7 a gastric and in 11 a duodenal ulcer had been demonstrated radiologically and had led to a gastrectomy in 12 (Table II); this included 6 of the 7 with gastric ulcer. In 10 patients this operation followed appreciable analgesic intake with an

TABLE I.—GASTROINTESTINAL DISORDERS IN 32 PATIENTS WHO ABUSED ANALGESICS

Gastric ulcer	7*
Duodenal ulcer	11
Upper gastrointestinal tract bleeding, no ulcer demonstrated	4
Symptoms suggestive of ulcer, none demonstrated	4
Gastrectomy	12*

*Does not include one patient who had an ulcerating carcinoma of stomach.

average ingestion before gastrectomy of 6 kg. of ASA. The decision to perform gastrectomy was made because of bleeding in six patients and resistance to treatment in three; in three the reason could not be determined. Thirty-seven per cent of those abusing analgesics had had a gastrectomy; this figure compares with 9% for those who had a more moderate but regular consumption and with 4% for those who denied appreciable intake.

Biochemical Studies

Liver function tests.—Serum bilirubin, glutamic oxaloacetic transaminase, lactic acid dehydrogenase and alkaline phosphatase values were each increased in three of 26 patients tested; two of the three had cirrhosis demonstrated by biopsy and were among the 12 of this group of 26 who were known to suffer from chronic alcoholism. The prothrombin time was elevated in four of 12 tested; thymol and cephalin cholesterol flocculations were both abnormal in one patient (of 14 tested) and bromsulphalein (BSP) retention was increased in one of seven.

Serum uric acid.—The mean value for 24 patients was 5.4 mg. per 100 ml.; three had elevated values recorded and two had a concentration of 3 mg. per 100 ml. or less.

Blood sugars.—The fasting blood sugar was elevated in four of 28 patients (slightly in three) and the 2-hour p.c. sugar in six of 17; of the latter six patients, three had had a subtotal gastrectomy. One other patient with increased a.c. and p.c. blood sugars had long-standing diabetes mellitus.

Hematology

Hemoglobin values ranged from 6 to 16 g. per 100 ml. with a mean lowest value of 11 g. and a mean value at the time of interview of 13 g. Twelve had values of 11 g. per 100 ml. or less recorded at some time; all were known to have had gastrointestinal blood loss except one, who suffered from pyelonephritis and renal failure.

White blood cell counts and differential studies were not abnormal.

TABLE II.—RELATIONSHIP OF ANALGESIC CONSUMPTION TO FREQUENCY OF GASTRECTOMY

	No. of patients	*Gastrectomies*		*Site of ulcer*	
		No.	*%*	*Gastric*	*Duodenal*
Excessive use	32	12*	37	6	6
Moderate consumption	151	14	9	2	12
Denied consumption	317	14	4	2	12

*Does not include one patient with carcinoma of stomach.

Evaluation of Urinary Tract

Bacteriology.—Urine culture was performed on 25 patients. Six had a moderate or heavy growth of organisms recorded on one or more occasions. Infection appeared to follow instrumentation in three patients and prostatectomy in one; one patient was paraplegic.

Proteinuria.—Thirteen of the 32 patients had proteinuria recorded. In 11 this was approximately 10 mg. per 100 ml.; values were 20 and 40 mg. per 100 ml. in the remaining two.

Urinary sediment.—Of the 32 patients, six had slightly increased erythrocyte excretion and in one hematuria was gross. Thirteen patients were considered to have increased leukocyte excretion, slight in seven and moderate in six. Casts were observed in the urinary sediment of 15 patients. These were described as rare or occasional in 10 and as one to four per low-power field in five. Hyaline and hyalogranular casts predominated; granular casts were observed in five patients. One patient had gross papilliuria on several occasions, confirmed histologically.

Renal function, pyelography and pathology.—Blood urea nitrogen and serum creatinine values were significantly elevated in two of 32 and 26 patients respectively; one had advanced cirrhosis of the liver and the other extensive papillary necrosis associated with an estimated consumption of 15 kg. phenacetin and 20 kg. ASA.

A more detailed investigation was made in 20 patients who were receiving their usual type and dose of analgesics. Renal function tests performed on all patients included creatinine clearance (12- or 24-hour collections), urinary osmolal concentrating capacity after at least 16 hours' water restriction (repeated after 10 units of aqueous vasopressin (Pitressin) given subcutaneously in five) and an ^{131}I hippuran renogram. Urinary phenolsulfonphthalein (PSP) excretion was measured in 17 patients and ability to acidify urine was evaluated in 15 (after 0.1 g. per kg. ammonium chloride if urine pH was not < 5.0).[9] Double-dose intravenous pyelography combined with tomography was performed in each case, as was an assay of urinary alkaline

phosphatase and lactic dehydrogenase (LDH).[10] Tissue was obtained for study of histology by biopsy in five patients who had pyelographic abnormalities and at autopsy in one.

The creatinine clearance, 15-minute PSP excretion and urinary alkaline phosphatase activity were abnormal in four patients; three were unable to acidify urine to pH 5.0 with arterial blood pH below 7.3 and in two, urinary LDH activity was elevated. Renograms were considered abnormal in six patients (peak after 5 minutes and/or fall to $< 60\%$ from peak by 20 minutes)[11] and eight were unable to concentrate urine to > 750 mOsm. per kg. following 16-hour water restriction; three of the latter also failed to do so following vasopressin (Pitressin). Intravenous pyelograms demonstrated extensive papillary cavities in one patient and some evidence of papillary necrosis according to the criteria of Lindvall[12] in six. Histological evidence to suggest an early phase of medullary necrosis or sclerosis[13-15] was found in three patients and advanced cortical interstitial nephritis in another.

Renal function tests, intravenous pyelograms and activity of urinary enzymes were all normal in 10 of the 20 patients; the remaining 10 had abnormalities in one or more of these tests. Four patients with demonstrated histological abnormalities failed to concentrate urine to 750 mOsm. per kg. and had pyelographic evidence to suggest papillary necrosis; three of these, including the one patient with severe impairment of renal function, had elevated urinary alkaline phosphatase activity and impaired acidification; in two urinary LDH activity was increased. The average consumption of phenacetin by these four patients was 14 kg. compared with 6 kg. for all patients abusing phenacetin-containing analgesics. Abnormalities in four other patients could be explained on the basis of some other disease process, including hypertension in two, generalized arterial disease in one and diabetes mellitus in one. Renal function tests were normal in all four patients who took ASA only.

DISCUSSION

Problems in Obtaining Accurate and Representative Data

The data related to quantities of analgesics consumed and duration of intake must be considered in the light of difficulties in obtaining an accurate history. These include limitation of memory for details five to 20 years in the past, the striking tendency for some abusers to minimize or even deny intake, possible fear of change in pension status if abuse of analgesics became known and potential exaggeration of intake by a few patients. Although consumption figures and related patient groups may have limited accuracy, a clear-cut history was required before including a patient in the group of 32 who were considered to abuse analgesics. There may, however, have been others who belonged in this group.

Because of the male bias, one should not necessarily consider these results representative of findings in a general hospital. Although analgesic consumption, abuse and associated renal disease all appear to be considerably greater problems in the female,[6, 16-19] this factor may have been partially offset by the high incidence of chronic illness and of abuse of alcohol and other drugs among this group, disorders which might be expected to be associated with a high incidence of excessive use.

Infrequency of ASA Abuse

A striking feature emerging from this study was the infrequency with which ASA itself was abused compared with mixed analgesics, particularly APC and C preparations. Only three patients taking ASA alone had consumed 5 kg. or more of ASA compared with 16 in the group taking mixed analgesics. Possible reasons include the superior analgesic effect of the mixed preparation, the stimulatory effect of caffeine, an undetermined effect of phenacetin in large amounts and the influence of codeine. We have recently seen typical withdrawal symptoms in two patients evidently addicted to codeine which they obtained largely from the consumption of some 40 tablets a day, each containing 8 mg. Codeine is not available in over-the-counter analgesic preparations in the United States as it is in Canada.

Analgesic Consumption Trends and Per Capita Intake

Consumption of analgesics has increased rapidly in many countries, with rates exceeding population growth.[2] Data from the Dominion Bureau of Statistics[3, 4] for a 20-year period (Fig. 3) indicate Canadian consumption trends for ASA, phenacetin and codeine. These analgesics are not manufactured in Canada. A continuation of recent trends, which suggest consumption to be increasing two to three times as fast as the population growth rate, may be expected to be accompanied by a rising incidence of associated complications.

Annual per capita consumption figures for phenacetin (Table III) are of interest, but must

TABLE III.—ANNUAL PER CAPITA CONSUMPTION OF PHENACETIN

Country	*Year*	*g. per year*
Australia[1]	1961	40
Denmark[1]	1956	25
Switzerland[64]	1957	23
South Africa[19]	1962	12
Scotland[42]	1963	12
U.S.A.[21,22]	1965	<10
Canada[3]	1965	6-7

be considered in the light of the fact that only a small segment of the population grossly abuses analgesics. Canada appears low on the list. Levin *et al.*[19] have quoted a figure of 22 g. for the United States; however, the origin of this statistic which is attributed to Moeschlin[20] is obscure and a maximal figure of 10 g. obtained by combining 1965 production of all analgesics and antipyretics other than ASA[21] with imports[22] would seem to be more accurate. The amount of ASA produced and imported in 1965 for U.S.A. consumption appears to have been more than seven times the figure for phenacetin;[21, 22] the relative amounts consumed in Canada would appear to be similar (Fig. 3).

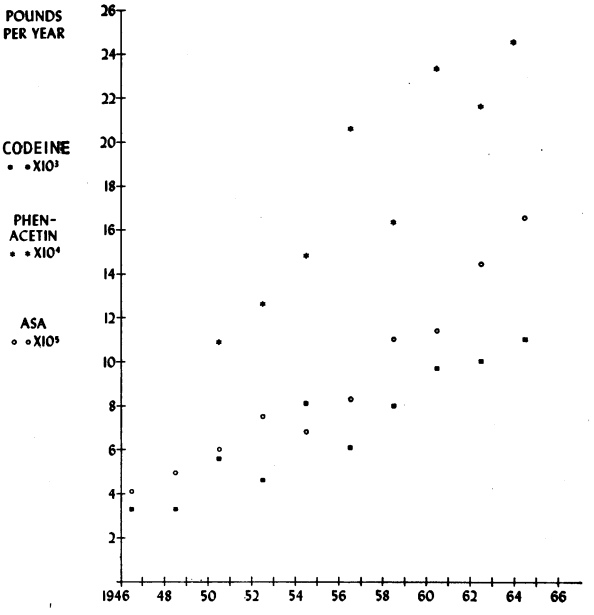

Fig. 3.—Estimated Canadian consumption as indicated by two-year means for acetylsalicylic acid and codeine imports,[4] and phenacetin used by the pharmaceutical industry.[3] Canadian population increased from 12.3 million in 1946 to 19.6 million in 1965.[65, 66] (Reproduced by kind permission of *The Canadian Scientist*, 2: 20, 1967.)

Liver Function Tests, Serum Uric Acid and Blood Sugar

In the absence of control data, firm conclusions cannot be made concerning the possibility of an effect of excessive use of analgesics on liver function, serum uric acid or blood sugar; however, considering the many factors involved, such as alcoholism, liver disease, gastrectomy and impairment of renal function, no clear influence was apparent in the parameters evaluated.

Psychiatric Abnormalities

The high frequency of psychiatric disorders found in those abusing analgesics has been a most striking feature. This observation has been made by several authors in patients found to have renal disease associated with analgesic abuse.[16, 17, 23-26] Habituation to alcohol and other drugs was a common association among the abusers in this series, and personalities were frequently of the immature and dependent type. It would seem likely that many of these individuals have a psychiatric problem which plays an important role in the production of the symptomatology for which analgesics are taken (e.g. headaches), and in the development of abuse.

Headache

Headache was the commonest primary reason given for consumption among the 32 patients who took excessive quantities of analgesics (56%), as it was among the 151 patients who took moderate amounts (70%). A review of nine studies and 185 patients who had renal disease associated with excessive use of analgesics[26] similarly demonstrates the high incidence of headache (76%) as the primary symptom leading to excessive analgesic intake. The headaches are most often described as a feeling of tension, fullness or heaviness in the head. It is possible that headache may occur with phenacetin toxicity[20, 27, 28] and after withdrawal of caffeine.[29]

Upper Gastrointestinal Abnormalities

Peptic ulcer, frequently leading to gastrectomy (Tables I and II), was very common in the group abusing analgesics. Douglas and Johnston[30] have commented on the common association between peptic ulcer and the use of analgesics containing ASA, an association which has also been common in patients reported with renal disease associated with analgesic abuse.[5, 16, 26, 32, 33] The failure of authors to mention peptic ulceration in several series of such patients who ingested analgesics not containing ASA[6, 12, 30, 34, 35] provides some evidence that salicylates may be the important analgesic ingredient in ulcer genesis and continuing activity. Gastric ulcers appear to be particularly common among analgesic habitués (Table II).[16, 26, 30] Psychiatric abnormalities may have been of primary importance in some patients

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with peptic ulcer; however, it seems likely that this factor contributed more often indirectly to ulcer genesis by leading to analgesic abuse. It must also be noted that seven of the 12 patients who underwent gastrectomy were chronic alcoholics, and two apparently took analgesics to relieve pain due to ulcer.

There is a large literature concerning the relationship of ASA to upper gastrointestinal bleeding,[36-41] and it has been suggested that caffeine may also be injurious to gastric mucosa.[42, 43]

The morbidity associated with the gastrointestinal complications of the misuse of APC-type analgesics would seem to exceed considerably that associated with involvement of the urinary tract.

Anemia

Several factors may be involved in the anemia associated with abuse of analgesics containing ASA and phenacetin, including gastrointestinal blood loss, renal failure and shortened red cell life span. The latter may be associated with antibodies to a red cell–phenacetin complex,[44] reduced glucose-6-phosphate dehydrogenase[45] and probably an adverse effect on red cell metabolism.[46] Splenomegaly may be present.[47] ASA may rarely cause anemia unrelated to bleeding.[48]

In this study, gastrointestinal blood loss was clearly the dominant factor in causing anemia, although malabsorption following gastrectomy may have been contributory in some patients.

Anemia has been present in most patients reported with renal disease associated with excessive use of analgesics; it frequently antedates the onset of azotemia, or its severity is out of proportion to the degree of renal failure.[16, 18, 26, 31]

Heinz bodies,[20] aberrations in red cell morphology[49] and the presence of methemoglobin and sulfhemoglobin[50] may be associated with anemia due to ingestion of phenacetin. We have found sulfhemoglobin, which persists for some time after drug withdrawal, to be a particularly useful diagnostic aid in patients who deny or minimize abuse. Severe methemoglobinemia following ingestion of phenacetin may be related to a defect in the metabolism of this drug.[51]

Renal Disease

Nephropathy associated with heavy consumption of analgesics was first described in Europe in 1953[52] and in North America in 1960.[28] The nephrotoxic potential of analgesics has recently been emphasized[6, 13, 14, 16, 18, 53] and reviewed;[2, 26, 54] these publications present a full picture of the clinical features, pathology and possible pathogenetic mechanisms of this form of renal disease.

The seriousness with which public health authorities have viewed this problem is reflected by passage of legislation to control the sale of phenacetin since 1960 in Sweden, Denmark, Switzerland, the U.S.A. and Australia. In Canada, since 1965, preparations containing phenacetin must bear a statement on the package that injury may result from prolonged excessive intake.

Disagreement continues on the importance of excessive use of analgesics as a cause of clinical renal disease.[55] Evidence from animal experiments must be considered inconclusive[54] and the toxic effects and actions of individual analgesics and of their combinations on the kidney are not fully known; therefore it may be considered premature to incriminate a single drug. Nevertheless, of the close to 2000 patients with nephropathy associated with excessive consumption of analgesics reported from a dozen countries,[2, 26] almost all took large quantities of phenacetin in combination with other analgesics. Total phenacetin consumption per patient in several series[6, 16-18, 26, 35] has averaged 7 to 8 kg. taken over 10 to 15 years, along with an equal or greater quantity of ASA in many instances; this is the equivalent of about 50,000 tablets of the usual mixed analgesics containing phenacetin available in North America, and the great majority of patients have taken five tablets a day for five years.[13, 26] Renal disease associated with chronic salicylate ingestion alone has been reported so infrequently that the association may be considered coincidental.

It is evident from this and other studies that many patients take large quantities of analgesics containing phenacetin without developing apparent renal disease. Sorensen[56] reviewed the incidence of renal disease found "in patients consuming analgesics" in eight European studies: percentages varied from 1 to 57, with an average of 22. Differences in population groups, selection criteria and definitions of renal disease render comparison of these studies difficult. In this study only one of the 32 patients considered to be taking excessive quantities of analgesics had serious renal damage attributable to these drugs, and three others of 20 studied in detail had pyelographic, histologic and functional evidence suggestive of early analgesic nephropathy, in the absence of other known etiological factors. This contrasts with a total of 22 patients found with serious renal disease associated with abuse of analgesics at the Queen Mary Veterans' and Royal Victoria hospitals over a four-year period.[26] At least 22 other cases have been re-

ported in Canada[23, 32, 57, 57a] and 73 in the U.S.A.[27, 47] The diagnosis of analgesic nephropathy obviously should not be made without a thorough investigation to exclude other forms of renal disease.

The factors which determine whether an individual will develop renal damage after a given dose have not been established, but may include the rate of consumption, the development of pyelonephritis, the presence of a pre-existing renal disorder, the presence of impurities and possibly genetic variations in drug metabolism; an example of the latter abnormality has been described for phenacetin where severe degrees of methemoglobinemia followed ingestion of the drug.[51] It remains possible that analgesic neuropathy is not a single entity.[58]

The tendency to substitute N-acetyl-p-aminophenol (NAPA), the chief excretory product of phenacetin, for aspirin alone or for phenacetin in mixed analgesics, must be viewed with some suspicion from the point of view of nephrotoxicity. Although NAPA may have some advantages,[59] papillary necrosis has been reported with excessive use,[60] it depresses oxygen utilization by the renal cortex *in vitro*[61] and it has been shown in hydropenic dogs to be concentrated in the medulla in concentrations up to 10 times that in the cortex.[62] The latter study also demonstrated that hydration prevented the medullary gradient, suggesting that it may be wise for patients taking phenacetin or NAPA regularly on a long-term basis to increase their fluid intake.

Syndrome of Analgesic Abuse

Although features of renal disease may dominate the clinical picture of the patient who abuses analgesics, these frequently appear only after many years and are often preceded by a long history of psychiatric disorder and headache, and the more recent onset of upper gastrointestinal complaints and anemia. All these disorders occur associated with excessive use of APC-type analgesics often enough in the same patient to warrant referring to this symptom complex as a syndrome,[26] certain aspects of which have been previously emphasized.[5, 16, 63] The results of this study support such a concept and the suggested common sequence of events in its development.

Use of the term syndrome would seem justified if it helps draw attention to complications at an earlier stage of development, hopefully eliminating the need for gastrectomy or the development of fatal renal failure in some patients. It is important that the majority of patients can be persuaded to stop the excessive use of APC-type analgesics;[26] therefore the major complications of abuse, including analgesic nephropathy, must in general be considered preventable. It appears that the nephropathy, even when moderately advanced, in many cases can be arrested.[26]

Further education of the public and the medical profession may produce some beneficial results. However, legislation may be required to control advertising, limit the sale of certain analgesics to prescription, or to provide stronger warnings. In addition much research, including epidemiological, psychiatric, pharmacological and biochemical studies, will be necessary if the many unanswered questions related to habituation, toxicity and relative potency of individual analgesics and their combinations are to be clarified.

The extensive and increasing use and abuse of analgesics make the frequently associated complications an important public health problem.

Summary Five hundred consecutive patients admitted to Queen Mary Veterans' Hospital were interviewed concerning analgesic consumption, and their records were examined. One hundred and ten admitted taking regularly the combination of aspirin, phenacetin, caffeine and in almost all instances codeine (APC and C). Seventy-three took aspirin (ASA) alone. Thirty-two patients were considered to have taken excessive quantities (an average of five or more tablets a day for at least three years). Headache was given as the major reason for taking analgesics by 18 and arthritis by seven; 18 had had a gastric or duodenal ulcer which had led to gastrectomy in 12, an incidence nine times that found among peptic ulcer patients not taking analgesics; 18 had been treated in a psychiatric ward and 13 were considered to be chronic alcoholics; 12 had hemoglobin values of 11 g. per 100 ml. or less, all but one of whom had had gastrointestinal blood loss. Intravenous pyelography and sensitive renal function tests were performed on 20 of the 32; four showed pyelographic changes and some reduction in renal function (marked in one case) which could be attributed to excessive APC and C intake, an etiology also suggested by the histological findings. Using the blood urea nitrogen as a criterion, only one of the remaining 12 had seriously reduced renal function and he had advanced cirrhosis of the liver. Twenty-eight of the 32 took APC and C; their average total consumption was 6 kg. of phenacetin and 8 kg. of ASA.

Résumé On a interviewé 500 anciens combattants entrés consécutivement au Queen Mary Veteran's Hospital, au sujet de leur consommation d'analgésiques et on a étudié leurs dossiers. Cent-dix ont reconnu prendre régulièrement l'association aspirine-phénacétine-caféine (APC) et,

dans presque tous les cas, de la codéine (C). Parmi ce groupe, 73 prenaient de l'aspirine (ASA) seule. Chez 32 malades, on a constaté une consommation excessive (moyenne d'au moins cinq comprimés par jour, pendant au moins trois ans). La raison principale donnée pour justifier l'ingestion d'analgésiques était la céphalée chez 18 malades et l'arthrite chez sept autres; 18 malades avaient eu un ulcère gastrique ou duodénal (opéré chez 12 malades), cette fréquence étant neuf fois plus élevée que celle qui avait été notée parmi les ulcéreux ne prenant pas d'analgésiques; 18 avaient été traités dans une salle de psychiatrie et 13 étaient considérés comme des alcooliques chroniques; 12 avaient un taux d'hémoglobine de 11 g par 100 ml ou moins, tous ces sujets sauf un ayant présenté auparavant une hémorragie gastro-intestinale. Chez 20 des 32 malades, on a pratiqué une pyélographie intraveineuse et des épreuves sensibles de la fonction rénale. Quatre malades présentaient des modifications pyélographiques et une certaine diminution de la fonction rénale (prononcée dans un cas), anomalies qui pouvaient être attribuées à l'ingestion excessive d'APC et de C. Cette étiologie était du reste suggérée par l'examen histologique. En prenant comme critère l'azote uréique, un seul des 12 malades qui restaient avait une diminution sérieuse de la fonction rénale et il présentait en outre une cirrhose hépatique avancée. Vingt-huit des 32 malades prenaient APC et C: leur consommation moyenne avait été de 6 kg de phénacétine et de 8 kg d'ASA.

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REFERENCES

1. ROSS, P.: *Med. J. Aust.*, **2**: 539, 1962.
2. SHELLEY, J. H.: *Clin. Pharmacol. Ther.*, **8**: 427, 1967.
3. (a) Canada, Bureau of Statistics, Industry and Merchandising Division: Medicinal and pharmaceutical preparations industry, 1950-59, Queen's Printer, Ottawa, 1952-61.
   (b) *Idem*: Manufacturers of pharmaceuticals and medicines (formerly the medical and pharmaceutical preparations industry); annual census of manufacturers, 1960-63, Queen's Printer, Ottawa, 1962-66.
4. Canada, Bureau of Statistics, External Trade Division: Trade of Canada; Imports by Commodities, monthly publication, vols. 3 to 22, 1946-1965 inclusive, Queen's Printer, Ottawa.
5. OLAFSSON, O., GUDMUNDSSON, K. R. AND BREKKAN, A.: *Acta Med. Scand.*, **179**: 121, 1966.
6. BENGTSSON, U.: Analgesic nephropathy: chronic pyelonephritis. *In*: International congress of nephrology, vol. 2, edited by G. E. Schreiner, sponsored by the International Society of Nephrology and other medical societies, S. Karger, Basel, 1967, p. 291.
7. SCHWEINGRUBER, R.: *Schweiz. Med. Wschr.*, **85**: 1162. 1965.
8. SCHREINER, G. E.: Effect of phenacetin on renal function of patients with a history of analgesic abuse. *In*: Progress in pyelonephritis, edited by E. G. Kass, F. A. Davis Company, Philadelphia, 1965, p. 347.
9. WRONG, O. AND DAVIES, H. E. F.: *Quart. J. Med.*, **28**: 259, 1959.
10. GAULT, M. H. *et al.*: *Brit. J. Urol.*, **39**: 296, 1967.
11. WALSH, E. L. AND MURDOCK, H. R., JR.: *Amer. J. Med. Sci.*, **252**: 224, 1966.
12. LINDVALL, N.: *Acta Radiol. (Stockh.)*, Suppl. 192: 5, 1960.
13. BURRY, A. F., DE JERSEY, P. AND WEEDON, D.: *Med. J. Aust.*, **1**: 873, 1966.
14. KINCAID-SMITH, P.: *Lancet*, **1**: 859, 1967.
15. CLAUSEN, E. AND JENSEN, K.: Renal biopsies on patients with a large abuse of analgesics. A histological and bacteriological investigation. *In*: Abstracts of the 3rd International Congress of Nephrology. II. Free communications, 1966, p. 171.
16. DAWBORN, J. K. *et al.*: *Quart. J. Med.*, **35**: 69, 1966.
17. TAN, G. H., RABBINO, M. D. AND HOPPER, J., JR.: *Calif. Med.*, **101**: 73, 1964.
18. PRESCOTT, L. F.: *Lancet*, **2**: 1143, 1966.
19. LEVIN, N. W. *et al.*: *S. Afr. Med. J.*, **36**: 555, 1962.
20. MOESCHLIN, S.: *Schweiz. Med. Wschr.*, **87**: 123, 1957.
21. United States Tariff Commission: Synthetic organic chemicals: United States production and sales of medicinal chemicals (preliminary), Washington, November, 1966, p. 2.
22. United States Bureau of Census: U.S. imports for consumption and general imports, TSUSA (tariff schedules of United States annotated) commodity and country, annual, 1966, Washington, 1967.
23. RAPOPORT, A., WHITE, L. W. AND RANKING, G. N.: *Ann. Intern. Med.*, **57**: 970, 1962.
24. HARVALD, B.: *Amer. J. Med.*, **35**: 481, 1963.
25. LARSEN, K. AND MOLLER, C. E.: *Acta Med. Scand.*, **164**: 53, 1959.
26. GAULT, M. H. *et al.*: *Ann. Intern. Med.*, In press.
27. YOUNG, J. V. *et al.*: *Ibid.*, **62**: 727, 1965.
28. MOOLTEN, S. E. AND SMITH, I. B.: *Amer. J. Med.*, **28**: 127, 1960.
29. GOODMAN, L. S. AND GILMAN, A.: Pharmacological basis of therapeutics, 3rd ed., The Macmillan Company, New York, 1965, p. 363.
30. DOUGLAS, R. A. AND JOHNSTON, E. D.: *Med. J. Aust.*, **2**: 893, 1961.
31. JACOBS, L. A. AND MORRIS, J. G.: *Ibid.*, **2**: 531, 1962.
32. RAMSAY, A. G. AND WHITE, D. F.: *Canad. Med. Ass. J.*, **92**: 55, 1965.
33. FIFIELD, M. M.: *New Eng. J. Med.*, **269**: 722, 1963.
34. LINDENEG, O. *et al.*: *Acta Med. Scand.*, **165**: 321, 1959.
35. NORDENFELT, O. AND RINGERTZ, N.: *Ibid.*, **170**: 385, 1961.
36. DOUTHWAITE, A. H.: *Brit. Med. J.*, **1**: 1143, 1938.
37. DOUTHWAITE, A. H. AND LINTOTT, G. A. M.: *Lancet*, **2**: 1222, 1938.
38. HURST, A.: *Brit. Med. J.*, **1**: 768, 1943.
39. MUIR, A. AND COSSAR, I. A.: *Lancet*, **1**: 539, 1959.
40. DAVISON, C., HERTIG, D. H. AND DEVINE, R.: *Clin. Pharmacol. Ther.*, **7**: 239, 1966.
41. Annotation: *Lancet*, **2**: 460, 1967.
42. BOYD, E. M. *et al.*: *Canad. J. Physiol. Pharmacol.*, **43**: 995, 1965.
43. PFEIFFER, C. J. AND GASS, G. H.: *Canad. J. Biochem.*, **40**: 1473, 1962.
44. MACGIBBON, B. H. *et al.*: *Lancet*, **1**: 7, 1960.
45. PRANKERD, T. A. J.: *Clin. Pharmacol. Ther.*, **4**: 334, 1963.
46. GOODMAN, L. S. AND GILMAN, A.: Pharmacological basis of therapeutics, 3rd ed., The Macmillan Company, New York, 1965, p. 334.
47. FORDHAM, C. C. AND HUFFINES, W. D.: *New Eng. J. Med.*, **277**: 749, 1967.
48. WIJNJA, L., SNIJDER, J. A. M. AND NIEWEG, H. O.: *Lancet*, **2**: 768, 1966.
49. DE LEEUW, N. K. M., SHAPIRO, L. AND LOWENSTEIN, L.: *Ann. Intern. Med.*, **58**: 592, 1963.
50. GOODMAN, L. S. AND GILMAN, A.: Pharmacological basis of therapeutics, 3rd ed., The Macmillan Company, New York, 1965, p. 332.
51. SHAHIDI, N. T.: *Amer. J. Dis. Child.*, **113**: 81, 1967.
52. SPÜHLER, O. AND ZOLLINGER, H. U.: *Z. Klin. Med.*, **151**: 1, 1953.
53. HARROW, B. R.: *J. Urol.*, **97**: 203, 1967.
54. HALEY, T. J.: *J. New Drugs*, **6**: 193, 1966.
55. SORENSEN, A. W. S.: *Nephron*, **3**: 366, 1966.
56. *Idem*: Effect of analgesic agents on renal function. A consecutive study by means of 24-hour endogenous creatinine clearance. *In*: Progress in pyelonephritis, edited by E. G. Kass, F. A. Davis Company, Philadelphia, 1965, p. 312.
57. LAKEY, W. H.: *Canad. Med. Ass. J.*, **85**: 477, 1961.
57a. KOCH, B. *et al.*: *Ibid.*, **98**: 8, 1968.
58. GILMAN, A.: *Amer. J. Med.*, **36**: 167, 1964.
59. Leading Article: *Brit. Med. J.*, **1**: 1083, 1965.
60. KRIKLER, D. M.: *Ibid.*, **2**: 615, 1967.
61. STAUB, H.: In discussion: Kuschinsky, G.: Phenacetin and kidney damage. *In*: Phenacetinabusus und Nierenschädigung. (Symposium in Freiburg im Breisgau, January 25, 1958.) Edited by H. Sarre, A. Moench and R. Kluthe, Georg Thieme Verlag KG., Stuttgart, 1958, p. 47.
62. BLUEMLE, P. W., JR. AND GOLDBERG, M.: *Clin. Res.*, **15**: 351, 1967 (abstract).
63. PRESCOTT, L. F.: *Lancet*, **2**: 91, 1965.
64. PLETSCHER, A.: *Bull. Schweiz. Akad. Med. Wiss.*, **14**: 100, 1958.
65. Canada, Bureau of Statistics, Census Division: Vital statistics. 1964: preliminary annual report, Queen's Printer, Ottawa, 1965.
66. Canada, Bureau of Statistics, Census Division: Population estimates (age and sex), 1921-1952, DBS Reference Paper No. 40, Queen's Printer, Ottawa, 1953.