Benzyl-imidazoline has been found to have a more lasting vasodilator effect than other drugs commonly employed for this purpose. It has an elective affinity for the smaller arteries and arterioles of the fingers and hands and toes.

It is relatively non-toxic, but may produce certain unpleasant side-effects, which can usually be avoided by suitable gradation of dose.

It is outstandingly successful in the treatment of Raynaud's disease and of appreciable value in that of intermittent claudication of arteriosclerotic origin.

It should not be used for the treatment of arterial hypertension.

The weight of evidence is that it is of little value in thromboangiitis obliterans, but even here it is worthy of trial.

We express our thanks to Messrs. Ciba Laboratories Limited for the generous supply of priscol for these tests.

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FACTORS ASSOCIATED WITH PERFORATION IN PEPTIC ULCER

BY

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AND

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This article records the results of a study designed to determine the factors associated with the development of perforation of peptic ulcers, and in particular to see if it is possible to predict the imminence of this complication.

The material consists of all cases of perforated peptic ulcer admitted to the Royal Victoria Infirmary, Newcastle-upon-Tyne, during the one-year period February 1, 1948, to January 31, 1949. In this time 189 patients were admitted. All, except two who came to necropsy, were treated surgically, consequently the diagnosis was confirmed in every case. Each patient was seen by one of us within a few days of admission and a detailed history was taken by following a set questionnaire. Thus, in addition to the patients' own statements, each was asked the same leading questions, and the moment of perforation was such a dramatic event that, almost without exception, they retained a vivid memory of what they were doing at the time and immediately before it. A full history was not obtained, however, in three critically ill patients.

Sex Incidence.—Of the 189 cases, 177 were males and 12 were females. Thus the male-to-female ratio is 14.8:1, which is much greater than the same ratio for peptic ulcer as a whole, which Tidy (1945) has given as 3.6:1. We have collected figures from the literature showing that of 1,349 cases of perforated peptic ulcer only 51 occurred in women, giving a ratio of 26.4:1. Therefore it would appear that not only is peptic ulcer less common in women but that, when present, the liability to perforation is considerably less than in men. Table I shows the age distribution in decades, the mean age, and the standard deviation for both sexes. It indicates that perforation is rare under the age of 20, but has a fairly even distribution in other decades.

TABLE I.—Age Incidence

Age in Years	No. of Male Cases	No. of Female Cases
Under 20	0	0
20-29	36	0
30-39	40	2
40-49	40	5
50-59	38	3
60-69	15	2
70-79	7	0
80 and over	1	0
Total	177	12
Mean age	44.5 ± 1.1	49.3 ± 2.9
Standard deviation ..	14.3	10.0

Occupation.—Thirty-five patients (18.5%) had jobs entailing a degree of responsibility which in our opinion was at least equivalent to that usually held by a foreman. This figure may be significant, for only 5% of the population served by this hospital have employment with a similar amount of responsibility.

Personal Factors.—An inquiry was made into some of the personal habits of the patients during the month which preceded perforation. The results of this are listed as follows:

Unusual cause of worry (e.g., employment, housing, or domestic difficulties)	33 cases
Unusually long hours of work	47 "
Irregular and hurried meals	58 "
Moderate smokers	116 "
Heavy smokers (over 20 cigarettes a day) ..	55 "
Heavy drinkers (over 4 pints (2.3 litres) of beer each night or 15 pints (8.5 litres) at the week-end)	20 "

History

Previous Perforation.—A history of previous perforation was obtained in 22 cases (20 men, 2 women), and three of these had perforated twice before their present admission. Therefore 11.6%, or 1 in 8.6 cases in this series, had had a recurrent perforation. Pearce (1932) analysed the reports of 4,813 cases of perforated ulcer and found only 33 instances of recurrent perforation—an incidence of 0.69%, or 1 in 145 cases. The information in our series was deliberately sought by direct questioning, and it may be that recurrent perforation is more common than hitherto supposed.

Previous Haemorrhage.—A history of previous gastrointestinal haemorrhage was obtained in 13 cases (6.9%).

Length of History.—Table II shows the duration of preceding gastric symptoms. It was once thought that most ulcers which perforated were acute or of recent origin. It will be seen from Table II that 129 cases (68%) had

TABLE II.—Duration of Symptoms

No. of Cases	No. of Cases
No previous symptoms	13
Less than 1 week	4
1 week to 1 month	18
1 month to 1 year	22
1 to 5 years	46
5 to 20 "	61
20 to 30 years	15
30 to 40 "	6
Over 40 "	1
No information	3
Total	189

suffered from gastric symptoms for a year or more. This suggests that a long history has a definite bearing on the likelihood of an ulcer to perforate, and these figures support the view put forward by Gilmour and Saint (1932) that the older an ulcer becomes the more chance it has of perforating.

Type of History.—Those patients who gave a history of previous indigestion were divided into two groups (Table III), one comprising those with a typical ulcer history

TABLE III.—Type of History

Typical ulcer history	121 cases, 64.0%
Vague dyspepsia	52 " 27.5%
No previous indigestion	13 " 7.0%
No information	3 " 1.5%
Total	189 " 100%

(as judged by the usual criteria) and the other those with a history of vague dyspepsia. It has been emphasized by many authors that the majority of patients with a perforated ulcer give a history of previous indigestion. The proportion of these cases in our series, however, is higher than that of other observers—a fact which can probably be explained by our method of taking histories a few days after operation. The patient by this time is more likely to recall some old complaint than he would be just after admission.

Symptoms Preceding Perforation

In 135 cases (71.4%) an exacerbation of symptoms occurred immediately preceding the perforation. The duration of these symptoms is shown in Table IV. In

TABLE IV.—Duration of Exacerbation

	No. of Cases		No. of Cases
Less than 1 week	58	5-6 weeks	1
1-2 weeks	30	Over 6 weeks	12
2-3 "	13	No information	2
3-4 "	15		
4-5 "	6	Total	137

most of these cases it was a fortnight or less. In 66 patients (49% of the 135 cases) the symptoms were definitely worse than those usually experienced, and in 87 patients (64% of the 135 cases) the symptoms had a crescendo character.

In 52 cases (27.5% of the total number) perforation occurred without any previous warning symptoms. It has already been stated that 13 cases had no previous history of indigestion whatsoever, and that in them the perforation was the first indication of a peptic ulcer. The remaining 39 cases had suffered some form of indigestion in the past, but their perforation occurred at a time when they were apparently quite well. That as many as 27.5% of the cases should perforate in this way seems to us significant in view of the difficulty it might cause in diagnosis.

The type of pain, or other symptoms, occurring during the three days before perforation was inquired into more closely; the results are shown in Table V.

TABLE V.—Type of Pain

	No. of Cases
Pain constant	41
Pain intermittent	69
Pain absent	52
Other symptoms (e.g., nausea, heartburn, epigastric fullness, or heaviness)	25
No information	2
Total	189

Other complaints during this time were loss of appetite (75 cases) and vomiting (41 cases).

Many patients claimed to be following a diet even up to the time of perforation, but the standard of these diets varied so widely that we have not thought them worth consideration. Three cases, however, perforated while in hospital undergoing medical treatment for peptic ulcer.

Relation to Work and Posture

The activities of the patients at the moment of perforation are summarized in Table VI. A man's day may be roughly divided into three parts, of which one is spent in bed, one at work, and one according to his own interests. It will be noted from the figures above that the results closely follow this rough division, for 31.7% of the perforations occurred at work and 27% while in bed.

TABLE VI.—Activity at Time of Perforation

	No. of Cases		No. of Cases
At work	60	Walking or standing	63
Not at work	127	Sitting	52
No information	2	In bed (25 cases asleep)	51
		Straining	12
Total	189	Stooping	9
		No information	2
		Total	189

The question of straining at the moment of perforation was inquired into carefully, but only 12 patients admitted to this, and there was no instance of direct trauma to the abdomen. Corlette (1931) applied the laws of physics to this problem and showed that an increase in intra-abdominal pressure will not cause any strain on an ulcer.

Consideration of the figures quoted would not lead one to suppose that posture and physical activity were factors involved in the perforation of a peptic ulcer.

Relation to Preceding Meal

The time interval between the last meal and the acute pain of perforation is shown in Table VII.

TABLE VII.—Time Since Last Meal

	No. of Cases		No. of Cases
During or immediately after meal	16	5-6 hours	15
Within 1 hour	20	6-12 "	16
1-2 hours	23	12-24 "	3
2-3 "	30	Over 24 hours	4
3-4 "	39	No information	4
4-5 "	19		
		Total	189

When one allows for the fact that many cases perforated during the night and a long time after their evening meal, it will be seen that the fairly even distribution of cases in Table VII does not suggest that perforation is associated with any special phase of digestion.

Inquiries were also made about the type of food and the size of the last meal, but neither of these seemed to have any influence on the development of perforation.

Month, Day, and Hour of Perforation

Seasonal Incidence.—Attempts have been made by several authors to assign a seasonal incidence to the development of perforation. Griswold and Antoncic (1941) for example, showed that the greatest number of their cases occurred in the spring. Hinton (1931) found an increased frequency in the spring and autumn months, and Berson (1942) described a mild seasonal variation with a relative infrequency of cases in the summer. The best study of this question has been carried out by Jamieson (1947), who investigated all the cases treated at the three main Glasgow hospitals over a period of 22 years. He found that the incidence was uniform throughout the spring and summer but fell off strikingly in the autumn, to rise again to a peak in the winter.

The monthly incidence in our cases is shown in Table VIII. No significance can be attached to the monthly variation in such a small number of cases, but it may be noted that the number in the autumn months is considerably less than in any other season.

TABLE VIII.—Monthly Incidence

	No. of Cases		No. of Cases
February	12	August	10
March	17	September	9
April	25	October	12
May	16	November	21
June	12	December	17
July	14	January	24
			189

TABLE IX.—*Day of Perforation*

	No. of Cases		No. of Cases
Sunday	20	Thursday	22
Monday	34	Friday	31
Tuesday	24	Saturday	32
Wednesday	26		
		Total	189

Day of Perforation.—Table IX shows the day of the week on which the cases perforated. The figures reveal no significant daily variation, and so fail to support Jamieson's contention that perforation of a peptic ulcer is relatively uncommon on Sundays and Mondays.

Hour of Perforation.—A record was made of the time of day at which perforation occurred, and the results are given in Table X. This shows that perforation is nearly

TABLE X.—*Time of Day of Perforation*

	No. of Cases
Midnight to 6 a.m.	37
6 a.m. to 12 noon	31
12 noon to 6 p.m.	55
6 p.m. to midnight	66
	121

twice as common in the afternoon and evening as in the morning.

Site of Ulcer

In a few cases the surgeon found difficulty in locating the ulcer accurately. The pyloric vein and other landmarks are not always clearly visible at operation, and it may be difficult to decide whether a pyloric ulcer is gastric or duodenal. The probable site was decided by the surgeon, and the numbers of each type of ulcer are shown in Table XI.

TABLE XI.—*Site of Ulcer*

Site	Males	Females	Total
Duodenum { Anterior wall ..	137	4	145 (76.7%)
{ Posterior wall ..	4	0	
Stomach { Lesser curve ..	12	4	43 (22.8%)
{ Pyloric antrum ..	23	4	
Jejunum	1	0	1 (0.5%)
Total	177	12	189 (100%)

These results show that in men perforation of a duodenal ulcer is four times as common as perforation of a gastric ulcer. In women perforation of gastric ulcers preponderates in the ratio of 2:1. The number of female cases, though small in comparison with the males, shows a reversal of the ratio of duodenal to gastric ulcers which is of statistical significance.

Discussion

Perforated peptic ulcer is a common condition in the North-east of England, and the admission to one hospital of 189 cases in a period of one year has afforded an unusually good opportunity of studying the circumstances associated with this event.

Various factors which have been thought to play a part in the aetiology of perforation were investigated, and some which were previously recognized have been confirmed. Thus we found a great preponderance of males and a high incidence of duodenal ulcers, although in women a significant difference was observed in that gastric ulcers were twice as common as duodenal ulcers.

It is interesting to note, too, the high percentage (18.5%) of patients who had employment entailing responsibility, and the very similar percentage (17.5%) who admitted to having some recent worry. However, these did not prove to be the same patients, and so, although responsibility, with the worry it entails, plays an accepted part in the aetiology of peptic ulcer, it does not seem to be implicated in the aetiology of perforation.

Investigation of the personal habits of the patients showed that 29% were heavy smokers and 10% were heavy drinkers, and the vast majority of the latter proved to be heavy smokers as well. We do not know the incidence of those who indulge heavily in tobacco and alcohol in this area, but we do not believe it to be as high as this. However, neither of these habits could be correlated with the onset of perforation, for in every case the patients had been indulging in them for years. This was also true in the case of the 31% of patients who admitted to taking hurried and irregular meals. Consequently, although these factors may be involved in the aetiology of peptic ulcer, or are, perhaps, common habits in the type of individual who develops a peptic ulcer, they do not appear to be of importance in our present study. Furthermore, the actual moment of perforation did not seem to be associated with physical activity or straining, the position of the patient, or any particular phase of digestion.

We had hoped that, as a result of our investigation, it might be possible to define a recognizable pattern of symptoms preceding perforation and so enable the medical practitioner to predict its onset, but our inquiry has not yielded information of this nature. During the three days before perforation 28% of the patients had no gastric symptoms whatsoever, 37% complained of intermittent abdominal pain, 22% of constant pain, and 13% of vague complaints such as nausea, heartburn, and a sense of fullness. If a doctor had visited these patients shortly before perforation occurred it is unlikely that he would have been able to anticipate the approaching disaster in the great majority of cases. Constant pain for several days, especially if becoming progressively worse, may be a warning of perforation; but this symptom is not specific, for it occurs during an exacerbation of ulcer symptoms without perforation.

Our study has led us to conclude that perforation is an unpredictable complication of peptic ulcer. In the majority of cases it will follow a recognizable period of indigestion or ulcer pain, associated perhaps with loss of appetite and vomiting, but in an appreciable number of cases there will be no warning symptoms whatsoever.

Summary

A total of 189 consecutive cases of perforated peptic ulcer admitted to one hospital during the period of a year have been studied. Our interest was focused on certain factors thought to have a bearing on the aetiology of the condition and on the symptoms immediately preceding perforation.

The great preponderance of males and the high incidence of duodenal ulcers were confirmed. In men, perforated duodenal ulcer was four times as common as perforated gastric ulcer. In women, however, perforated gastric ulcer was twice as common as perforated duodenal ulcer.

In 91% of patients a history of previous indigestion was obtained: in 64% this conformed to a typical ulcer pattern. In 68% the history of indigestion lasted for longer than one year.

The onset of perforation seemed to be unrelated to individual habits of eating, drinking, and smoking, or to a particular phase of digestion, and the moment of perforation was not correlated with the position of the patient, straining, or physical activity.

Perforation occurred less often in the autumn than in the other seasons. The daily incidence varied little, but perforation was more frequent from midday to midnight than in the morning hours.

In the three days preceding perforation 22% of the patients had constant abdominal pain, 37% intermittent pain, 28% no pain, and 13% vague symptoms such as heartburn and nausea. There was no specific pattern of symptoms which led up to

perforation, and the latter seemed to be an unpredictable complication of peptic ulcer.

We would like to express our thanks to Professor F. H. Bentley and the surgeons of the Royal Victoria Infirmary for their kindness in allowing us to see their cases, and to Mr. H. Campbell for his help with the statistics.

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DENTAL CAVITIES IN THE GOLDEN HAMSTER

BY

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The reported production of caries-like lesions in the molar teeth of the golden hamster (Arnold, 1942) has aroused new interest in the quest for experimental animals of value to workers in the dental field. Subsequent investigators assumed that the tooth cavities observed in animals receiving rations rich in carbohydrate, especially sucrose, were analogous to those found in human caries (Keyes, 1944; Dale, Lazansky, and Keyes, 1944; Orland, 1946; Sognnaes, 1948; Hurst, Firsbie, Nuckolls, and Marshall, 1948; Granados, Glavind, and Dam, 1948; Shafer, 1949; Mitchell and Shafer, 1949). On the other hand, I have shown that hamsters given wholemeal flour, wheatmeal bread, or white maize as their main dietary ingredient develop a form of parodontal disease associated with calculus deposition and food impaction leading to primary cavitation of the cementum and dentine of the tooth roots (King and Gimson, 1948-9; King, 1949).

Later disease phases include extension of the cavities into the pulp, followed by breakdown of the coronal dentine and enamel; but disintegration of the tooth crown, with the appearance of caries-like cavities, is essentially secondary to the initial root excavations which themselves result from the periodontal disturbances. The present note summarizes the first of a series of studies on the effects of replacing the cereal of such diets by refined or raw cane sugar, thus bringing the investigations more into line with those of the American workers.

Material, Methods, and Results

The experimental animals, all males, were obtained from two different sources, the approximate diets of the parents and of the offspring till weaning being as follows:

Medical Research Council Farm (M.R.C.).—Bread soaked in water, 16 parts; bran, 6; fishmeal, 3; whole wheat, 16; milk powder, full cream, 4; green foods, varied, *ad lib*.

Messrs. May and Baker (M. and B.).—Ground yellow maize, 55 parts; wholemeal flour, 15; ground linseed, 15; casein, 4; dried yeast, 5; milk powder, full cream, 5; salt mixture, 1. (The salt mixture comprised calcium carbonate, 5; sodium chloride, 5; iron citrate, 1; potassium iodide, 0.02.)

The hamsters were then given the following basal diet from weaning for an experimental period of six months: sugar, 65 parts; casein, 22 parts; dried live yeast, 0.5 part; alfalfa, 5 parts; sodium chloride, 1 part; peanut oil, 0.5 ml. daily. Each hamster received 10 g. daily of this diet

moistened with about 10 ml. of water, and in addition 5 g. of cabbage and 5 g. of carrot twice weekly. The animals from each stock were divided into two groups, one receiving the refined white cane sugar as used in this country and the other a specially prepared sample of raw sugar (pol. 96), the approximate percentage composition of these products being:

	Sucrose	Invert	Ash	Water	Organic Material
Refined	99.95	0.01	0.01	0.02	0.01
Raw	96.00	1.20	0.60	0.02	0.01

The fluorine contents of the two varieties of sugar, estimated according to the method described in the report to the Medical Research Council's Fluorosis Committee (1949, Memo. No. 22), were refined, 0.36 p.p.m.; raw, 0.3 p.p.m. F. Before mixing with the other dietary ingredients, the particle size of the sugars was rendered similar by grinding to powder form.

The results given in Table I are based on the presence of definite tooth cavitation visible in radiographs magnified three times; in each instance they were confirmed by dissecting microscope examination ($\times 18$) of the tissues *in situ* with the aid of a fine exploratory broach.

TABLE I.—Incidence of Dental Cavities in Hamsters: Radiographic and Dissecting Microscope Observations

Stock Origin	Type of Sugar in Experimental Diet	Animals			Molar Teeth		
		Total Observed	Affected		Total Present	Affected	
			No.	%		No.	%
M.R.C.	Refined	20	8	40.0	240	14	5.8
	Raw	20	4	20.0	240	4	1.7
M. & B.	Refined	26	12	46.2	312	20	6.4
	Raw	22	10	45.5	264	15	5.7

It is evident that no firm conclusions can be drawn from these findings. In the M.R.C. stock groups those given the refined sugar seem to have been rather more prone to tooth destruction than those receiving the raw sugar, but in the M. and B. hamsters the effects of the two sugars were closely similar. It is of course possible that the stock (pre-natal and pre-weaning) diet may have influenced the issue, but even if this were so there is still no explanation of the apparent difference between the two main groups.

In other respects, however, the results were by no means sterile. On x-ray diagnosis, there was a general but not always consistent tendency for the upper teeth to be more affected than the lower: taking all groups together, the percentage incidence figures for the two jaws were 3.8 and 1.1 respectively. Histological examination of the material disclosed a much higher incidence of both maxillary and mandibular lesions but little difference in their proportionate distribution. By radiographic and by histological diagnosis the upper third and second and lower first and second molars, in that sequence, were the most prone to destruction. This observation is of interest in view of the similar distribution of calculus-induced parodontal disease in hamsters on high cereal rations (King, 1949), but assumes still greater significance when the histopathology of the present lesions is considered.

Decalcified serial sections were made from 48 teeth of the M.R.C. groups showing radiographically definite or suspected cavities. Histologically, 32 cavities were found, and in all but two the initial lesion was clearly sited in the cementum of the tooth root, whence it progressed into the dentine and often into the pulp; with involvement of the latter, secondary disintegration of the coronal dentine and