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Possible dietary protective factors in relation to the distribution of duodenal ulcer in India and Bangladesh

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SUMMARY In India there are regions of high incidence and regions of low incidence of duodenal ulcer. Rats prefed for two weeks on diets from low incidence areas developed significantly fewer rumenal ulcers after pyloric ligation than rats fed on diets from high incidence areas. The protective action was found in various individual items of food taken from the diets of low incidence areas. Unrefined wheat and rice, certain pulses (black gram, green gram, horse gram), some millets (sava, kutki, ragi), soya bean, ladies' fingers, cabbage, spinach, and whole cream milk were protective. Refined wheat, polished rice, maize, cornflour, sorghum vulgare, sugar, bananas, amaranthus, brinjal, peanut oil, some pulses (Bengal gram, turdhal), and skimmed milk were non-protective. The protective factor seems to be either a lipid or a liposoluble substance which is active whether given orally or parenterally. Horse gram (*Dolichos biflorus*) is a particularly potent source.

The map in Fig. 1 shows the distribution of duodenal ulcer in India and Bangladesh. There are marked dietary differences between the areas of relatively high and low incidence.[1] In the lower incidence areas of North India (Punjab, Rajasthan, and parts of Madhya Pradesh, Uttar Pradesh, Haryana, and Himachal Pradesh) the staple food is unrefined wheat eaten as chappatis. In many areas, particularly the Punjab, the diet of unrefined wheat is supplemented by considerably more milk or milk products, pulses, and green vegetables than are eaten in the areas of high incidence.

In almost all of the high incidence areas the staple diet is refined polished rice. This is supplemented in some of the areas, especially Kerala, by variable amounts of manioc (cassava or tapioca). In a relatively dry belt of higher incidence running horizontally eastwards across Maharashtra, Northern Karnataka into Andhra Pradesh, the staple diet is the millet sorghum vulgare (jowar or cholam) with occasional rice. In some drier areas, such as in the Aravalli hills of Rajasthan where duodenal ulcer is common, the staple diet is maize.

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In addition to these broad differences in the distribution of duodenal ulcer there are interesting isolated areas of low incidence with peculiar dietary habits surrounded by rice eating areas of high incidence.

One such area is found in Orissa at Udaiyagiri where the Kond tribes living in the eastern ghats have a lower incidence of duodenal ulcer than the rice-eating Oriyas in the plains. The Kond's diet is seasonal, made up of a grass-like cereal called Kahari or Querry, the pulses Bengal gram and horse gram, mango seeds, jungle plants, and roots and mahula flowers.

Another area is that inhabited by the Gond tribes around Padhar in southern Madhya Pradesh. They use the millets sava (*Echinochola freemantacea*) and kutki (*Faricum millare*) cooked into chappatis.

A third area of relatively low incidence is found south of Mysore where for most of the year the staple diet is the millet ragi (*Eleucine coracana*). A low incidence is also reported in the drier hilly areas of Bihar where more millets and pulses are grown.

There are also isolated islands of high incidence surrounded by areas of low incidence. These islands have a moister climate and rice is grown as the staple food. Such areas occur around Simla and in the Kangra Hills, in Hoshiarpur, around Srinagar in Kashmir, and in the plains of Assam.

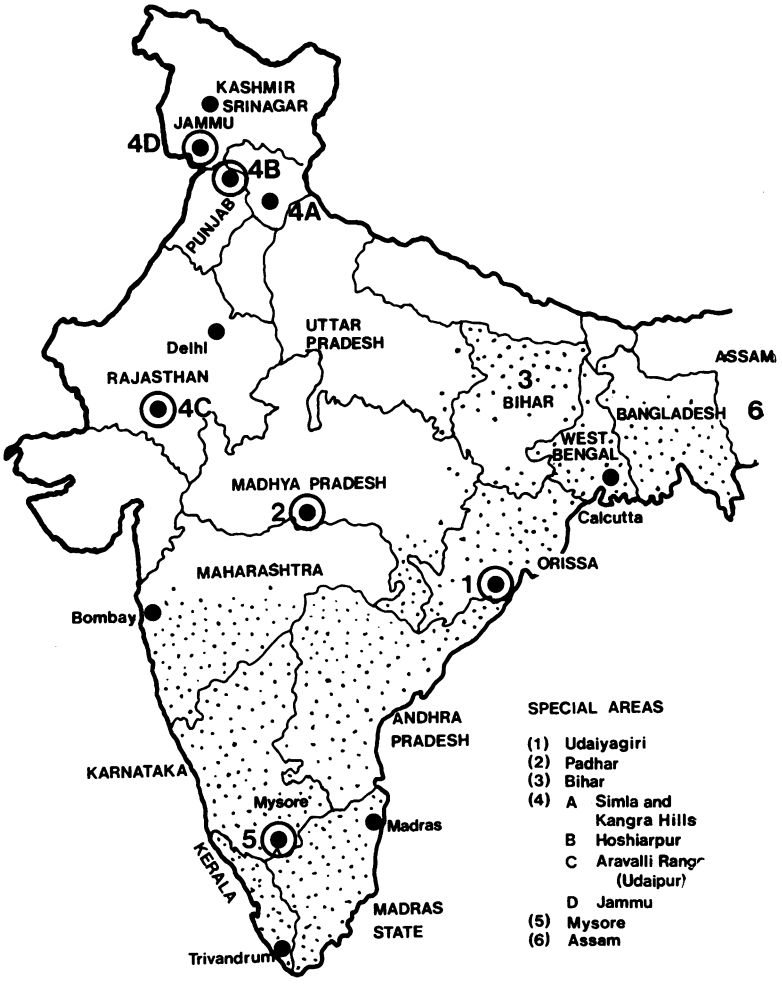

Fig. 1 *Map showing distribution of duodenal ulcer in India and Bangladesh. The areas of high incidence are stippled.*

The possibility that differences in diet might be factors of aetiological importance contributing to the differences in incidence of duodenal ulcer is supported by the report of Malhotra[2] in 1978. He described a group of 50 patients in Bombay with radiologically proven duodenal ulcers who were hospitalised until their ulcers were symptomatically and radiologically healed. After this, one half continued on their normal rice diet and one half changed to a Punjabi diet. At the end of five years 21 patients were left in each group. Among those on the Punjabi diet only three (13%) had relapsed in comparison with 17 (81%) of those on their normal rice diet.

These findings would support either the concept that there may be ulcerogenic factors in the diet of high incidence areas or protective factors in the diet of low incidence areas.

Methods

PYLORUS LIGATION EXPERIMENTS

The pylorus ligated rat was chosen as an acceptable model for investigating these possibilities because it is one that has already been widely used in testing ulcerogenic or anti-ulcer substances.[3] Female albino rats (Wistar strain), weighing 100–160 g, in batches of eight were fed on the required food substances for a period of two weeks. They were then isolated in a wire meshed cage to avoid coprophagy and given water only for 24 hours. A pyloric ligation[4] was then performed under ether anaesthesia. The stomach was washed out with 4 ml or more of normal saline until clean and then 2 ml of normal saline were left in the stomach. The rats were kept isolated and allowed access to water for six hours, at the end of which time they were again anaesthe-

Table 1 *Controls*

	Total no. of rats	*Rumenal ulcers*				
		No. of rats with ulcers	*Total no. of ulcers*	*Large ulcers*	*Perforations*	*Ulcer score*
South Indian (cooked)	16	16	68	19	9	4·25
South Indian (uncooked)						
1	8	8	33	10	4	4·1
2	8	8	35	9	5	4·4
3	8	8	37	14	4	4·6
4	8	7	25	9	4	3·1
5	8	7	20	9	2	2·5
6	8	7	27	6	5	3·4
7	8	8	16	5	3	2·0
8	8	8	11	6	2	1·375
9	8	8	25	6	2	3·1
10	8	8	17	5	2	2·1
11	8	8	27	4	3	3·4
12	8	7	30	4	2	3·75
13	8	8	18	4	2	2·25
14	8	8	20	5	2	2·5
15	8	7	25	6	5	3·1
16	8	8	38	12	3	4·75
17	8	8	32	8	4	4·0
18	8	8	23	12	3	2·9
19	8	7	27	6	5	3·4
Total (uncooked)	152	147	491	140	60	
		% with ulcers 96·7%		% of total ulcers 28·5%	% of total rats 39·5%	Mean ulcer score 3·2

tised. The oseophagus was ligated and the stomach. with contents, was removed. The stomach was opened and the number of macroscopic ulcers in the rumen were recorded, together with the number of large ulcers (>2 mm) and the number of rats with perforations. Histological sections were made also of the rumen and mucosa.

For comparison an 'ulcer score', obtained by dividing the total number of ulcers by the number of rats in the group, was used. A diet giving a score of more than 3 was regarded as non-protective, between 1 and 1·5 as moderately protective, and under 1 as highly protective.

CONTROLS

South Indian diet was used as the basic reference diet and at frequent intervals throughout the experiments batches of eight rats were fed on unaltered South Indian diet to constitute a control group. Altogether there were 152 rats in this group. The results are shown in Table 1.

COMPOSITION OF GROUPS

The experiments were done in four groups:

Group 1 This was a continuation of the experiments previously reported[5] comparing South Indian diet with Punjabi diet, plus additional experiments studying the effect of removing the pulses and/or vegetables from Punjabi diet.

Group 2 The effect was assessed of adding groups of food substances from Punjabi diet and items of food from the diets of the Kond and Gond tribes to South Indian diet.

Group 3 The effect was ascertained of adding a variety of other foodstuffs from high and low incidence areas to South Indian diet and also certain food substances available in both areas.

Group 4 The effect was assessed in a miscellaneous group of adding unrefined and refined wheat and unmilled rice, skimmed milk and whole cream milk powder, and also various oils to South Indian diet.

DETAILS OF DIETS

Group 1: Punjabi and South Indian diets

The composition of the Punjabi and South Indian diets expressed as percentage by weight was as follows:

Punjabi diet		*South Indian diet*	
Unrefined wheat flour	41·2		
Rice flour	5·7	Rice flour	78·5
Maize flour	8·6		
Pulses:			
Bengal gram 1·7	5·6	Turdhal flour	5·0
Green gram 1·7			
Black gram 1·7			
Lentils 0·5			
Green vegetables (leafy):			
Amaranthus	4·0	Amaranthus	2·1
Other vegetables:			
Potato	6·2	Potato	4·1
Ladies' fingers	6·2		
Banana powder	0·6	Brinjal	4·1
Vegetable fat (Dalda)	4·4	Groundnut oil	5·0
Sugar	9·5		
Corn starch	5·0		
Common salt	0·2	Common salt	0·3
Skimmed milk powder	2·9	Skimmed milk powder	0·9

Apart from some of the earlier experiments, the foodstuffs were given uncooked. The constituents of the diet were evenly mixed into a mash with boiling water. The rats showed no tendency to be selective in their eating. Although whole cream milk and its products feature in Punjabi diet it was decided to use skimmed milk powder in both diets to reduce the number of variables.

Group 2: Additives to South Indian diet from Punjabi, Kond, and Gond diets

(a) From Punjabi diet
Groups of substances:

1. Pulses	Bengal gram	1·7	5·6%
	Green gram	1·7	
	Black gram	1·7	
	Lentils	0·5	
2. Vegetables:	Amaranthus	4·0	17·0%
	Potato	6·2	
	Ladies' fingers	6·2	
	Banana powder	0·6	

3. Pulses and vegetables:
1 and 2 above in combination
4. Wheat (unrefined) 41·2% plus pulses and vegetables as above

(b) From the Kond tribe's diet
1. Kahari (Querry) 5%
2. Horse gram 5%

(c) From Gond tribe's diet
1. Sava 78·5% (in place of rice)
2. Kutki 78·5% (in place of rice)

Table 2 *Foodstuffs added to South Indian diet*

Corresponding control group	*Additives*	*%*	*Total no. of rats*	*Rumenal ulcers*				
				No. of rats with ulcers	*Total no. of ulcers*	*Large ulcers*	*Perforations*	*Ulcer score*
No.	*Group 3*							
	From low incidence areas							
	Punjab							
13	Pulses: Bengal gram	5	8	8	16	3	2	2
13	Pulses: Green gram	5	8	5	12	2	1	1·5
13	Pulses: Black gram	5	8	6	13	3	0	1·625
17	Pulses: Red gram	5	8	8	24	7	3	3·0
	Vegetables							
11	Ladies' fingers (mucilage)	10	8	5	5	1	0	0·625
	Chamarajnagar area							
7	Millet (ragi)	60*	8	7	10	3	1	1·25
	From high incidence areas							
	South India							
16	Cassava	60*	8	8	42	10	4	5·25
			8	8	41	10	3	5·12
			8	8	40	13	4	5·0
17	Sorghum vulgare	60*	8	7	16	5	1	2·0
	Vegetables							
Nil	Amaranthus (dried)	5	8	8	25	10	4	3·125
			8	8	22	9	5	2·75
12	Brinjal	5	8	8	26	3	1	3·25
14	Bananas							
	Raw	20*	8	8	22	4	3	2·75
	Cooked	20*	8	8	19	5	2	2·375
	Aravalli Range							
Nil	Maize							
	Coarse	60*	8	6	25	6	1	3·125
	Refined	60*	8	8	30	7	3	3·75
Available all areas								
	Vegetables							
Nil	Cabbage							
	Dried	5	8	4	6	2	0	0·75
	Fresh	5	8	6	8	2	0	1·00
17	Spinach	5	8	3	7	3	0	0·875
	Soya bean							
5	Cake	10	8	4	7	1	0	0·875
13	Flour	5	8	6	10	3	1	1·25
Nil	Sugar	10	8	8	32	6	2	4·0
	Group 4							
17	Unrefined wheat	78·5*	8	4	6	1	0	0·75
	Refined wheat	78·5*	8	8	22	8	1	2·75
Nil	Unmilled rice	78·5*	8	3	8	0	0	1·0
			8	2	11	1	0	1·375
	Milk powder							
Nil	Full cream	1	8	6	9	1	1	1·125
Nil	Skimmed	1	8	8	19	5	1	2·375
	Oils							
13	Soya bean	0·1 ml	8	2	4	0	0	0·5
7	Ragi	0·1 ml	8	7	7	3	1	0·875
7	Cowpea		8	7	13	4	2	1·625
Nil	Cotton seed		8	8	18	4	2	2·25

*In place of an equivalent amount of polished rice.

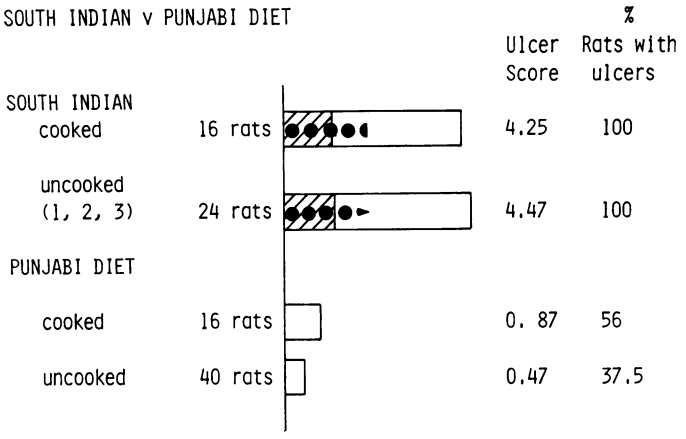

Fig. 2 *Comparison of the effect of two weeks' prefeeding with South Indian and Punjabi diet on rumenal ulceration after pyloric ligation. Key to Figures: Blank: ulcer score. Hatched area: percentage of large ulcers ●: number of perforations per batch of eight rats. (The number in parentheses shows the number of the corresponding control group).*

Groups 3 and 4—Details of these groups are given in Table 2.

Results

GROUP 1: PUNJABI V. SOUTH INDIAN DIETS

Figure 2 shows that Punjabi diet conferred a marked degree of protection when compared with South Indian diet. When the food is cooked there is no significant change in the number of ulcers with either diet.

Figure 3 shows that removal of the vegetables and pulses from Punjabi diet either singly or in combination removed its protective effect.

GROUP 2: ADDITION OF SUBSTANCES FROM PUNJABI DIET TO SOUTH INDIAN DIET

Figure 4 shows that, although adding the groups of pulses or vegetables alone did not give significant protection, combining them gave moderate protection, and adding 41·2% unrefined wheat gave marked protection.

ADDITION OF SUBSTANCES FROM KOND TRIBE'S DIET AND FROM GOND TRIBE'S DIET TO SOUTH INDIAN DIET

Horse gram from the Kond tribe's diet was highly protective, and the cereal Kahari (querry) modera-

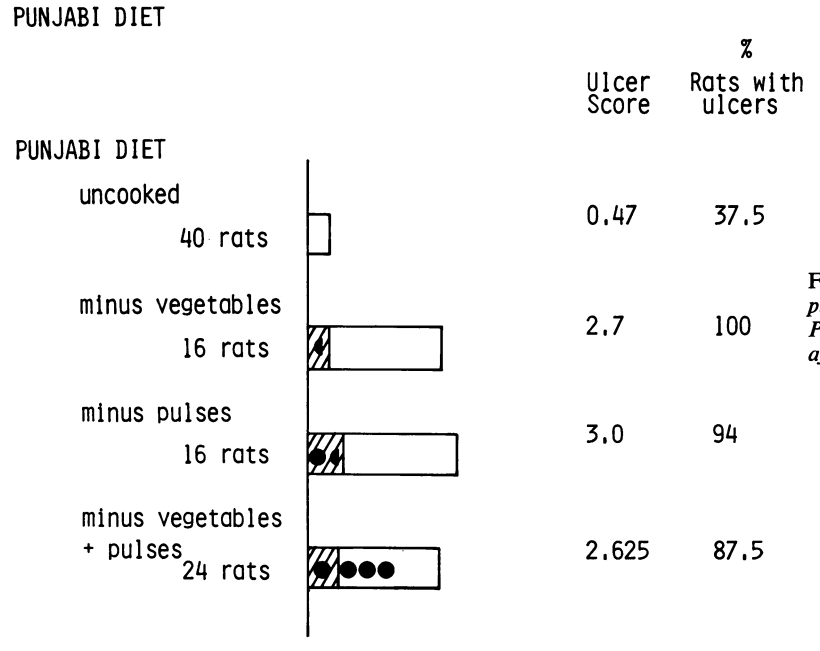

Fig. 3 *The effect of removing pulses and/or vegetables from Punjabi diet on rumenal ulceration after pyloric ligation.*

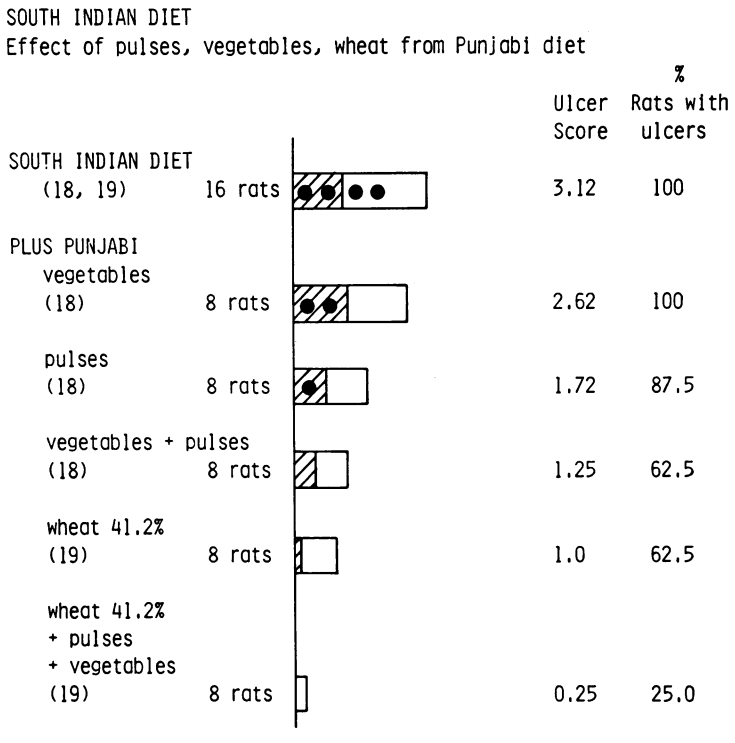

Fig. 4 *The effect of adding vegetables and/or pulses, and of wheat to South Indian diet on rumenal ulceration after pyloric ligation.*

tely protective. Bengal gram was not protective. These were given at the 5% level.

The millets sava and kutki from the Gond tribe's diet were highly protective at the 78·5% level.

GROUP 3: OTHER FOODSTUFFS ADDED TO SOUTH INDIAN DIET

From low incidence areas of duodenal ulceration

From the Punjab The pulses green gram and black gram were moderately protective. Bengal gram and red gram (*Kabuli sanna*) gave no protection.

The mucilage from ladies' fingers was protective.

From the Chamarajnagar area of Mysore The millet ragi was moderately protective.

From high incidence areas of duodenal ulceration

From South India Cassava and sorghum vulgare were non-protective. (Cassava increased the ulcer

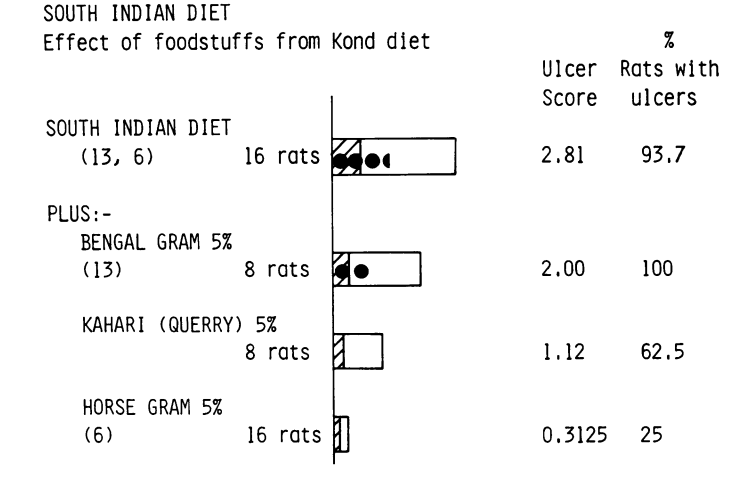

Fig. 5 *The effect of adding foodstuffs from Kond diet to South Indian diet on rumenal ulceration after pyloric ligation.*

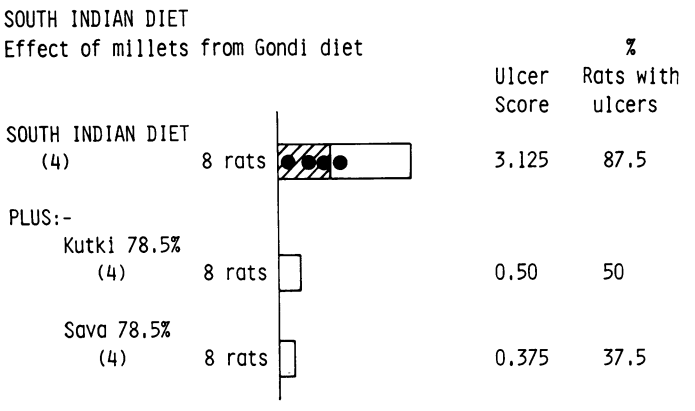

Fig. 6 *The effect of adding millets from Gondi diet to South Indian diet on rumenal ulceration after pyloric ligation.*

Table 3 *Pylorus ligation (prefeeding)*

	No protection	*Moderately protective*	*Highly protective*
Staple foods	Wheat—refined Rice—polished* Maize—unrefined* cornflour* Cassava* Sugar	Rice—unmilled	Wheat—unrefined†
		Kahari (Querry)†	
Millets	Cholam*	Ragi†	Sava† Kutki†
Pulses	Turdhal* Bengal gram Kabuli sanna	Green gram† Black gram†	Horse gram†
Beans			Soya bean
Green vegetables	Amaranthus* Lettuce		Cabbage Spinach
Other vegetables	Brinjal* Potato Banana*		Ladies' fingers†
Milk powder	Skimmed	Full cream†	
Oils	Groundnut* Cotton seed* Cowpea		Soya Ragi

*Foods from high incidence areas.
†Foods are from low incidence areas.

score.) The vegetables amaranthus, brinjal, and bananas (raw and cooked) were non-protective.

From the Aravalli range of Rajasthan Unrefined and refined maize (cornflour) were non-protective.
Available in high and low incidence areas The vegetables cabbage (dried and fresh) and spinach were highly protective. Soya bean cake was highly protective at the 10% level and soya bean flour moderately protective at the 5% level. Sugar was non-protective and increased the ulcer score.

GROUP 4: UNREFINED AND REFINED WHEAT AND UNMILLED RICE

Unrefined wheat was highly protective and refined wheat was non-protective. Unmilled rice was moderately protective.

Full cream and skimmed milk powder
Full cream milk powder gave moderate protection and skimmed milk powder gave no protection.

Various oils
Ragi oil and soya bean oil were highly protective, but

Table 4 *Ether extracts*

Corresponding control group (no.)	*South Indian diet plus ether extract (equivalent to: mg)*		*Total no. of rats*	*Rumenal ulcers*				
				No. of rats with ulcers	*Total no. of ulcers*	*Large ulcers*	*Perforations*	*Ulcer score*
	Millets							
10	Sava	220	8	7	12	3	0	1·5
	Kutki	200	8	5	9	3	1	1·125
	Horse gram							
6, 9	Orally	4·0	8	1	1	0	0	0·125
			8	1	2	0	0	0·25
11, 12	Intramuscularly	2·5	8	4	5	1	0	0·625
			8	3	3	0	0	0·375
6, 7	Orally: ether fraction from alcoholic extract		8	2	3	0	0	0·375
	(equivalent to 5 g% horse gram in diet)		8	2	3	1	1	0·375

groundnut, cowpea, and cotton seed oil gave no protection.

The findings are summarised in Table 3.

Histology

The sections of the mucosa and rumen in the rats with a high ulcer score showed multiple erosions and infiltration with inflammatory cells. The mucosa and rumenal epithelium of those with a low score were much thicker and normal looking. The mucosal cells were also rich in mucus, whereas those with a high ulcer score were almost devoid of mucus.

Discussion

The results show a good correlation with the geographical distribution of duodenal ulcer in India and suggest that many of the food substances peculiar to the low incidence areas may contain a protective factor. The protective effect of Punjabi diet would appear to be an accumulative effect and a result of the combination of several substances each with a moderate protective action: black gram, green gram, ladies' fingers, whole cream milk, plus unrefined wheat. (The findings with regard to wheat are discussed below.) In the Konds' diet, kahari is moderately protective and horse gram is highly protective. The millets, sava and kutki, in the Gonds' diet are protective. Ragi, the principal staple food of the low incidence area south of Mysore, is also moderately protective. Sorghum vulgare, the staple diet in some high ulcer incidence areas, is non-protective, and cassava, which features in the very high ulcer incidence area of Kerala, seems to be almost ulcerogenic.

The possibility of the presence of protective factors against peptic ulceration in naturally occurring food substances is supported by the action of carbenoxolone and also the deglycyrrhizinated fractions obtained from liquorice. Twenty years ago Cheney[6–8] showed that pre-feeding with several foodstuffs (cabbage, butter, egg yolk) conferred protection against experimental peptic ulceration in several animal models. Raw cabbage[6–9] was highly protective but its action varied with season and storage. The protective factor was thermolabile and destroyed by cooking. It was also liposoluble. It was from the lipid fraction of cabbage that Adami[10–12] eventually developed gefarnate, which has healing properties in peptic ulceration. Gefarnate was found to act systemically whether given orally or parenterally, whereas the action of carbenoxolone is topical.

The findings in this series of experiments support those of Cheney in confirming the protective actions of cabbage and whole cream milk even in powder form. The natural oils occurring in soya bean and ragi were protective. Ether extracts were made from some of the other foodstuffs which had proved protective—sava, kutki, and horse gram. The results are shown in Table 4. All showed some protection. This was most marked with horse gram, which was active in very small amounts when given either orally or by intramuscular injection for two weeks before pyloric ligation. These results and those of other fractionation experiments are being reported separately.

UNREFINED WHEAT

The findings with regard to unrefined wheat require further comment. At the 41·2% level and 78·5% it was protective when added to South Indian diet. It has yet to be explained why Punjabi diet deprived of its pulses and vegetables was non-protective, even though it contained unrefined wheat (after removal of the pulses and vegetables the proportion of unrefined wheat rises to 53%). It is postulated that the remaining maize, cornflour, and sugar may have an adverse non-protective effect. Both cornflour and sugar (Table 2) increased the ulcer score in a similar way to cassava when added to South Indian diet.

Conclusion

The overall findings support the hypothesis that there may be a dietary basis to account for the distribution of duodenal ulcer in India. It is postulated that, while in any community there are people with increased susceptibility to duodenal ulceration, the absence or presence of protective factors in the diet may determine whether or not they develop actual ulceration. The findings with regard to unrefined rice and wheat, and to sugar, lend support to Cleave's observations about the distribution and changing incidence of peptic ulcer.[15–16] The evidence obtained from pyloric ligated rats is being substantiated using other experimental models, and further fractionation is being done to identify the active principles. The hypothesis, if valid, needs to fit in with the geographical distribution and changes in incidence in other countries. Already it seems to fit in with the distribution in Java where duodenal ulcer is uncommon in the areas where soya bean is eaten with rice (personal communication). It may fit in with the Pacific islands where duodenal ulcers seem to occur only in the areas where taro is the staple food (taro is similar to cassava).[17–18] It may also fit in with the changing incidence and dietary habits in the United Kingdom with the varying consumption of refined carbohydrate, fresh vege-

tables, and milk. At the moment, however, no definite pattern has emerged from a study of diets in the high and low incidence areas of duodenal ulceration in Africa,[19] but much more information is still required.

If it is substantiated that certain foods do contain protective factors it will be important to determine whether the same factor may be present throughout and whether it is a lipid or a liposoluble substance. In the same way as Malhotra found that Punjabi diet prevented patients with healed duodenal ulcer from getting relapses, so it may prove possible that, at some time in the future, relapses may be prevented by taking a small dose of 'protective factor' and that horse gram (*Dolichos biflorus*) may prove to be a rich source of the factor. The same factor may be of use also in the treatment of peptic ulcer as a cyto-protective agent, perhaps in combination with H_2 antagonists.

Statistical analysis

A probability plot of the 60 groups of eight rats referred to in Tables 1, 2, 4 shows that the data fall into two main groups, those with a total score of less than 16—that is, average score per rat of 2—and those with a score of 16 or more. This suggests two groups of diets, the protective and the non-protective. Examination of the points at the extremities suggests oral horse gram to be very protective and cassava to be almost ulcerogenic.

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