that no fewer than 527 (5.27%) have one practically useless eye. This condition is colloquially known as "lazy eye." In 1% of all the patients examined one eye was registrably blind, in another 2% the eye had such poor vision as to be quite useless. In the remaining 2% of amblyopic patients the vision was so poor that binocular vision was absent. If this finding were extended to the population at large, it is apparent that, out of every 100 children born, between 5 and 6 are destined to lose the use of one eye.

This condition of unilateral amblyopia is well known throughout the civilized world as a source of wastage of man-power in times of national emergency. Its economic and social disadvantages are equally serious, especially should anything happen to the good eye.

An amblyopic patient is usually ignorant of his disability, relying unconsciously on his good eye. Unfortunately the condition develops in infancy and early childhood, and by the time the child starts school it too often has become permanently established.

In a country with the most comprehensive medical service in the world, it is paradoxical that its young children should be allowed to run the risk of suffering from this grave disability through neglect.

I thank Mr. N. P. R. Galloway and Mr. G. Gordon Napier for their kindness and encouragement, and numerous family doctor colleagues who kindly referred their patients to me, and who otherwise made this investigation possible. My thanks are due also to the editor of the *Journal of the American Medical Association* for special information on visual standards and problems in the U.S.A.

REFERENCES

- Burian, H. M. (1954). *A.M.A. Arch. Ophthalm.*, **51**, 509.
 — and Watson, C. W. (1952). *Ibid.*, **48**, 137.
 Burri, Clara (1942). *Arch. Ophthalm. (Chicago)*, **28**, 235.
 Campbell, Dorothy (1947). *Brit. J. Ophthalm.*, **31**, 321.
 Chavasse, F. B. (1939). In *Worth's Squint*, 7th ed. Baillière, Tindall and Cox, London.
 Clark, W. E. Le Gros (1941). *J. Anat.*, **75**, 225.
 Donders, F. C. (1864). *On the Anomalies of Accommodation and Refraction of the Eye*, translated by W. D. Moore. New Sydenham Society, London.
 Downing, A. H. (1945). *Arch. Ophthalm. (Chicago)*, **33**, 137.
 Duke-Elder, W. S. (1949). *Textbook of Ophthalmology*, vol. 4. Kimpton, London.
 Evans, J. N. (1929). *Amer. J. Ophthalm.*, **12**, 194.
 Feldman, J. B. (1941). *Arch. Ophthalm. (Chicago)*, **26**, 38.
 — and Taylor, A. F. (1942). *Ibid.*, **27**, 851.
 Guibor, G. (1944). *Amer. J. Ophthalm.*, **27**, 986.
 Irvine, S. R. (1948). *Trans. Amer. ophthalm. Soc.*, **46**, 527.
J. Amer. med. Ass., 1940, **114**, 29.
 Keith, N. M., Wagener, H. P., and Barker, N. W. (1939). *Amer. J. med. Sci.*, **197**, 332.
 King, J. H., and Passmore, J. W. (1955). *Amer. J. Ophthalm.*, **39**, 173.
 Peter, L. C. (1932). *Ibid.*, **15**, 493.
 Pugh, Mary (1954). *Brit. J. Ophthalm.*, **38**, 321.
 Theodore, F. H., Johnson, R. M., Miles, N. E., and Bonser, W. H. (1944). *Arch. Ophthalm. (Chicago)*, **31**, 399.
 Travers, T. àB. (1938). *Brit. J. Ophthalm.*, **22**, 577.
 Waardenburg, P. J. (1954). *Docum. ophthalm. (s'-Grav.)*, **7-8**, 422.
 Wald, G., and Burian H. M. (1944). *Amer. J. Ophthalm.*, **27**, 950.
 Worth, C. (1903). *Squint, Its Causes, Pathology and Treatment*. Bale, Sons, and Danielson, London.
 — (1921). *Ibid.*, 5th ed. Baillière, Tindall and Cox, London.

The *Handbook of Treatment of Acute Poisoning*, by E. H. Bensley and G. E. Joron, of the Montreal General Hospital (2nd ed., pp. 212; E. and S. Livingstone, Ltd., 15s.), is intended primarily for the physician with no special experience of toxicology who is called upon suddenly to treat cases of poisoning. It may also be used as a basis for lectures to students. Although it deals mainly with acute forms of poisoning, with the emphasis on emergency measures, some reference is made to chronic poisoning and the late effects of acute intoxications. A number of industrial poisons are included.

A REVIEW OF 300 PATIENTS WITH HAEMATEMESIS OR MELAENA

BY

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During the four years 1953 to 1956 inclusive, 300 patients with haematemesis or melaena were admitted to the Bristol Royal Infirmary: 14 were readmitted on one or more occasions, making a total of 321 admissions. Of these, 308 were emergency admissions, and the other 13 developed the haematemesis or melaena as in-patients. During the four-year period there were 9,355 medical admissions (both emergencies and from the waiting-list), so that haematemesis and melaena accounted for 1 in 30 of these.

Of the 321 admissions (Table I) the bleeding was attributed to a proved or presumed ulcer in 259 (81%). Treatment was medical in 224 cases (with 10 deaths) and was surgical in 35 (with 4 deaths); in most fatal

TABLE I.—*Diagnosis in 300 Patients with Haematemesis or Melaena*

	Ulcer Group						Other Causes	Total
	Gastric	Duodenal	"Peptic"	Anastomotic or Stomal	Acute Ulcer or Erosion	Total		
No. of patients	63	96	38	6	40	243	57	300
" " admissions	66	106	39	6	42	259	62	321
Emergency surgery	10	18	—	1	6	35	6	41
Surgical deaths	1	2	—	1	—	4	—	4
Total deaths	3	10	—	1	—	14	7	21

cases, however, death was not from haemorrhage. A cause other than ulcer was diagnosed in the remaining 62 admissions: this group (in which there were 7 deaths) is discussed below.

Before these results can be appraised it is necessary to consider various factors which may influence prognosis.

Age and Sex Incidence

Haematemesis or melaena becomes more common with advancing age (Fig. 1). The frequency increases steadily to the seventh decade; in the eighth and ninth decades the numbers are smaller; out of the whole series of 300, 134 (33%) were 60 years or over. (This increased frequency in the elderly applies both to the ulcer cases and to the others.)

Of the patients with ulcer there were 158 men and 85 women (Fig. 2). Below the age of 70 there were more than twice as many men as women (144 to

FIG. 1.—Age distribution of 300 patients with haematemesis or melaena from all causes. Those in whom the diagnosis was of some form of ulcer are shown below the interrupted lines.

61), but over that age women outnumbered men (24 to 14). This high incidence among men is found particularly in the group with duodenal ulcer (72 men and 24 women), to a less extent among those with gastric ulcer, and not at all amongst "peptic" ulcers and those with acute ulcer or erosions (Fig. 3). In particular it is in the group with bleeding from duodenal ulceration that men exceed women; this is so throughout the whole age range, with the difference increasing up to the seventh decade (Fig. 4).

Degree of Severity of Haemorrhage

In assessing how serious was a patient's haemorrhage, whether or not he survived is of little use. This is because with adequate treatment by blood transfusion and emergency operation death from haemorrhage is now quite rare, and death when it does occur is usually due to some associated disease or to advanced age (as is shown below). Probably the best indices of a severe haemorrhage are whether transfusion is needed and whether emergency surgery is needed. Those with coexisting perforation naturally form a more serious group.

It is often held that haemorrhage is more serious in the older male patients and in those who have previously had a haematemesis or melaena. In this series there were 166 admissions of men with bleeding from ulcer: in 114 this bleeding was the first attack, while in 52 there

TABLE II.—Admissions of Males with First Bleeds from Ulcer

	Age Group			Total
	-39	40-59	60+	
Total	19	54	41	114
Transfused	10	34	28	72
Emergency surgery	2	12	7	21
Perforation also	—	3	1*	4

* Not operated on.

TABLE III.—Admissions of Males with Previous Bleeds from Ulcer

	Age Group			Total
	-39	40-59	60+	
Total	12	15	25	52
Transfused	5	8	16	29
Emergency surgery	—	4	1	5
Perforation also	—	2	—	2

had been a previous episode of bleeding. The severity of the bleeding in these two groups is given separately in Tables II and III.

In Table II the details are given of coexisting perforation, of emergency surgery, and of blood

transfusion among those 114 admissions of men with no previous haematemesis or melaena: those who underwent emergency surgery numbered 2 of the 19 cases (5%) below the age of 40, while in the fifth and sixth decades there were 12 out of 54 (22%), and over 60 years of age 7 out of 41 cases (17%). (Blood transfusion was also more common in older age groups, but the increase is less marked and is not significant.)

In Table III the same details are given of those 52 admissions of men in whom there had been a previous episode of bleeding. As with those with no previous haemorrhage, the proportion undergoing emergency surgery is higher over the age of 40. In the two groups together (those with bleeding for the first time and those with previous bleeding), emergency surgery was undertaken in 2 of 31 (6%) below 40 years, in 16 of 69 (23%) between 40 and 59, and in 8 of 66 (12%) of 60 and over. On the other hand, these figures do not suggest that, in this series, previous bleeding was associated with any increased severity in this subsequent

TABLE IV.—Admissions of Females, All Bleeds from Ulcer

	Age Group			Total
	-39	40-59	60+	
Total	18	27	48	93
Transfused	11	19	26	56
Emergency surgery	1	1	7	9
Perforated also	—	—	2*	2

* Neither operated on.

haemorrhage for which they were then in hospital, for the proportion receiving blood transfusion and undergoing surgery was no higher than in those with no previous history of haemorrhage (Table II).

All told, there were 93 admissions of women with bleeding from ulcers (Table IV); 48 of these were 60 years of age and over and 7 had emergency surgery. (There were also 2 of 48 patients in this age group who had also a perforation; but neither was operated on.) Compared with men in this series it seems that, below the age of 60 at any rate, haematemesis and melaena in women was less often severe.

Nature of Emergency Operation and Findings

Of the patients eventually diagnosed as having haemorrhage from an ulcer, 35 underwent emergency surgery. In five there was an associated perforation; in four of these bleeding preceded the perforation, and partial gastrectomy was performed in three and local

FIG. 2.—Different age distribution in men and women with haematemesis or melaena in whom some form of ulcer was diagnosed.

FIG. 3.—Haemorrhage in men from duodenal ulcer was much commoner than in women. Those in whom the site of the ulcer was not determined ("peptic ulcer") and those with bleeding from acute ulcer were as common in women as in men.

FIG. 4.—Bleeding from duodenal ulcer becomes increasingly common in men until the seventh decade.

suture in the fourth; while in the fifth case perforation was treated by local suture and the haemorrhage followed three days later. There was no perforation in any of the remaining 30, and all had partial gastrectomy to control continuous bleeding.

Of the perforated ulcers, four were duodenal and one was gastric. In the 30 without perforation 7 had a gastric and 14 a duodenal ulcer, while 2 others had both; 6 had subacute ulcers or acute erosions; in the remaining case haemorrhage was from an anastomotic ulcer at the site of an old gastro-enterostomy.

Amongst the whole series of 321 admissions, there were six patients who were submitted to emergency operation and who were diagnosed as not having an ulcer. No cause was found in three of these; the gastric arteries were tied in one, and the abdomen was closed without any further intervention in the other two; and all three recovered.

Six other patients with ulcer underwent surgery (four having a partial gastrectomy) within one to four weeks of admission. As the bleeding had by then ceased and operation was performed for other reasons—for example, to exclude malignancy—these cases are all included among those treated “medically.”

Results of Treatment in Ulcer Group

Table V shows the results of treatment in the various age groups of men and women. There were 145 admissions of patients below 60 years of age: 125 were treated medically and 2 died, 20 were treated surgically and 3 died. There were 114 admissions of patients of 60 years or older: 99 were treated medically and 8 died, 15 were treated surgically and 1 died. Among the 166 admissions of men there were 11 deaths, compared with 3 deaths in 93 admissions of women.

TABLE V.—Results of Treatment in Bleeding Ulcers

Age Group	Admissions of Men					Admissions of Women				
	Total	Medical		Surgical		Total	Medical		Surgical	
		No.	Deaths	No.	Deaths		No.	Deaths	No.	Deaths
-39	31	29	—	2	—	18	17	1	1	—
40-59	69	53	1	16	3	27	26	—	1	—
60+	66	58	6	8	1	48	41	2	7	—
Totals	166	140	7	26	4	93	84	3	9	—

TABLE VI.—Deaths in Patients Whose Haemorrhage was from Ulcer

Sex	Age	Comment
<i>Medically Treated Cases</i>		
F	31	Previously five admissions for bleeds, and a partial gastrectomy. Massive haemorrhage
M	58	Died from chest infection
M	62	Pulmonary embolism
M	66	Second haemorrhage. Duodenal ulcer and gastric erosions
M	68	In heart failure after coronary. Bled first while in-patient
F	72	Coexisting perforation. Diagnosed, but unfit for surgery
M	77	Perforated after admission. Diagnosed, but unfit for surgery
F	77	Not diagnosed
M	78	Hypertension, coronary ischaemia. Heart failure
M	79	Also carcinoma of colon. Not transfused
<i>Surgically Treated Cases</i>		
M	54	Haematemesis after admission for hypertension. Successful partial gastrectomy. Stroke four weeks later
M	56	Peritonitis after partial gastrectomy for bleeding anastomotic ulcer
M	59	Bled 4 days after closure of perforation. Subphrenic abscess. Massive haemorrhage from gastric erosion
M	61	Bled from peptic ulcer after recent abdominal perineal resection for carcinoma; gastrectomy, further haemorrhage

Causes of Death

The causes of death in patients with ulcer are given in Table VI. In two cases treated medically and in two other cases in surgical hands the principal or only cause was haemorrhage itself. An associated illness or cardiovascular accident accounted for four others of those medically treated; but the haemorrhage may have predisposed or contributed to death in these cases. In three other medical cases, all over 70 years of age, there was an associated perforation, and in two of these who were judged to be unfit for surgery it is reasonable to attribute to the blood loss part of the shock which rendered these patients unfit for surgery. Of the four deaths among the patients treated surgically, further haemorrhage was the cause in two: in one of these cases, however, the surgery was suturing of a perforated ulcer, and the subsequent bleeding was from fresh acute erosions.

Causes of Haemorrhage or Melaena other than Ulcer

In about one-fifth of the patients in this series the haematemesis or melaena was attributed to some cause other than ulcer: out of the total of 300, there were 57 such patients (Table I and Fig. 5) and they accounted for 62 admissions.

Portal hypertension (10 cases) caused bleeding in all age groups, while bleeding from hiatus hernia (13 cases) occurred only in the middle-aged and elderly.

FIG. 5.—The diagnoses made in 57 patients who bled from causes other than ulcer.

Although cancer of the stomach is common it was a rare cause of haematemesis or melaena in this series, there being only five cases. Amongst the group of nine patients shown as “various” are included haemophilia, Schönlein’s purpura, uraemia (3 cases), volvulus of the stomach, and an intestinal neuroma. No diagnosis was made in 17 patients. As already mentioned, even at emergency operation no cause was discovered in three; in a fourth no lesion was seen at gastroscopy, and in a fifth who died from a stroke 10 days after admission no intestinal lesion was found at necropsy.

Emergency operations were performed in 4 of the 10 patients with portal hypertension; this was oesophageal transection and ligation in two, portacaval anastomosis in one, and splenectomy with partial gastrectomy in the fourth. All recovered, though one patient died (from haemorrhage) on a later admission. This was the only death from bleeding; of the six other patients who died, four had cancer, one was in uraemia, and one had a stroke.

Seasonal Incidence

Over the four years there were more admissions during the winter: 44 in December, 41 in January, and

30 in February. There were least in the summer: 21 in June and 15 in July. Fig. 6 shows this rhythm; each column represents the total admissions for the month: above the break is the number in the ulcer group, below the break is the number in which bleeding was due to some other disease. (Our hospital records are indexed by the date of discharge or death and not by the date of admission, so that, in fact, the present series consists of patients discharged or dying between January 1, 1953, and December 31, 1956. Therefore, all patients admitted in, say, December, 1952, and who remained in hospital until 1953, are included in this series, whereas those who were admitted in, say, December, 1956, and who were still in-patients on January 1, 1957, have not been included.)

Discussion

Two great advances in medical treatment of haematemesis have been, first, that of adequate fluids by mouth championed by Meulengracht (1935), and, secondly, the use of slow drip blood transfusion introduced by Marriott and Kekwick (1935); the value of

FIG. 6.—Admissions for haematemesis or melaena were more common in the winter months of December, January, and February, and least common in the summer.

these two principles of treatment was clearly proclaimed by Avery Jones (1947). Less surely established is the role of emergency surgery, and the purpose of this present review was partly to collect evidence about this.

It is widely recognized that, whatever the treatment, the results in haematemesis are profoundly affected by age, and to a less extent by sex and the nature of the underlying lesion. Moreover, the epidemiology of ulcer varies in different parts of the country, and changes as time goes by. So to enable our results to be compared with those of others, both published and in future, this information about our patients has been included in this report.

Effects of Age

The incidence of peptic ulcer increases with age until about 55 (Doll, Jones, and Buckatzsch, 1951), and the steady rise in haematemesis is in keeping with this. After that age the incidence of ulcer decreases (Doll *et al.*, 1951), though haematemesis, at least in this series, becomes more common. In Fig. 1 the numbers in the eighth and ninth decades are fewer, but, of course, the number is also lower in the general population, and if allowance is made for this the incidence in all the groups over 60 is constant.

In the 1951 census 16% of the population were 60 years old or more, so the proportion of 33% of that age group in our series reflects an actual prevalence of bleeding in the elderly. There is also a steady increase in the elderly in the general population. The effect of these two factors may be seen in the observation of Avery Jones (1957) that the numbers of those over

60 years in his very large series have been increasing in recent years: thus there were 33% between 1941 and 1946, 38% between 1947 and 1951, and 40% in 1952 to 1954.

Amongst the elderly haematemesis and melaena prove to be much more dangerous than in those who are younger. In the experience of Lewin and Truelove (1949) the death rate in those without previous haematemesis was only 5.1% for those under 50, compared with 29% for those above that age. Avery Jones (1957) in his larger series showed a sharp increase in mortality at 60: in the period 1951 to 1954 this mortality for all ulcer cases under 60 years was only 2%, compared with 16.5% for those over that age. In our series the results in the corresponding age groups are 3.4% and 9%.

It is acknowledged that the reason for the increased mortality in the older age groups is not that the bleeding is more severe, for death from haemorrhage is most unusual, but rather that it is largely due to associated diseases, particularly chronic chest diseases, and the high incidence of complications after admission such as pulmonary embolism and urinary or other infections (Avery Jones, 1956). The facts in Table VI provide ample support for this generalization. All the same, a haemorrhage in an elderly patient must contribute to the death in many of these cases; the accompanying fall in blood pressure must be more serious when there is coronary or cerebral atheroma; and, as Gunz, Gebbie, and Dick (1954) have shown, timely transfusion is often of benefit in these patients when they develop symptoms of insufficient coronary blood supply.

Sex

The different incidence of bleeding from ulcer in men and in women conforms with the different prevalence of the ulcers. Thus the relative immunity of women to ulcer until the menopause (Doll *et al.*, 1951) is reflected in the corresponding lower incidence of haematemesis over the same span (Fig. 2). There is a higher incidence of chronic ulcers in men, but the incidence of acute erosions in the two sexes is equal (Avery Jones and Pollack, 1945); likewise in the present series, bleeding from the various lesions seems to be distributed amongst the sexes according to the same pattern (Fig. 3).

Our results in women were better than in men (3 deaths out of 93, compared with 11 out of 166); that this was not entirely due to chance is suggested by the results of Avery Jones (1956), who also found them to be better in women. Why this should be is not certain, but in our series less use was made of blood transfusion and of emergency surgery in women, so the haemorrhage itself seems less often to have been severe.

Previous Bleeding

It used to be believed that a previous episode of bleeding indicated that the patient's ulcer was likely to be deep and scarred and haemorrhage might more readily persist. More recently Lewin and Truelove (1949) found that a history of previous haemorrhage had no bearing on the immediate outcome. As stated above, it seems that the outcome is of little value in assessing the severity of a patient's haemorrhage, because very few of our patients died from haemorrhage. Those with severe haemorrhage now have transfusions

and, if need be, undergo surgery. If these procedures are good evidence of severity there is no indication (Tables II and III) that a history of previous haemorrhage made matters any more serious. As a corollary these same criteria support the conclusion of Lewin and Truelove (1949) that the worse results in the older age groups are not related to a higher frequency of previous haemorrhage.

Emergency Surgery

Among the 259 admissions for bleeding from ulcers there were 14 deaths (5.4%). This figure is as low as has been achieved elsewhere. The results do not seem to be due to a favourable selection of patients, for the composition of the series is materially much the same as that of Avery Jones (1957) except that we had slightly fewer old patients. In 35 of the 259 admissions (13.5%) an emergency operation was done, and in 33 of these the procedure was partial gastrectomy. In men between 40 and 59 years old the proportion undergoing operation was 23%. Fraenkel and Truelove (1955) reported that the death rate in their series has fallen from 18.8% to 5.6%, and attribute this to their increased use of emergency surgery; they now treat as many as one in six patients by emergency operation. Ogilvie, Cardoe, and Bentley (1952) reported that in their cases, where the proportion treated surgically has been 10%, the mortality was 5%. Avery Jones (1957), however, has found no fall in the overall mortality since emergency partial gastrectomy was introduced as a policy, though he is convinced that there is good reason for this operation in selected cases.

From the causes of death (Table VI) it is apparent that in our series more frequent surgery could not be expected to reduce the mortality much further.

As emergency partial gastrectomy carries its own risk, it is self-evident that the best results can be achieved only when patients selected for surgery are all those who would have a worse prognosis if they were treated medically. The criteria that have been laid down to guide others when to operate vary a little in detail, but the principles are the same. Thus, continued bleeding after 24 hours in hospital is used as a criterion by Ogilvie *et al.* (1952) (though some might feel this rather rigid); Avery Jones (1957), from his own experience and that of others, adopted a policy whereby operation was performed "especially on patients with known chronic ulcer whose age was over 40 and who had a brisk recurrent bleeding after admission."

In this series there has been no question of a uniform policy adopted alike by all physicians or surgeons; but it is a principle to seek surgical opinion early in any severe haematemesis, and for both the medical and the surgical attendant to review the need for surgery if bleeding continues or recurs. An essential part of this treatment has proved to be the routine use of the 15-minute pulse chart and the careful instruction of the nursing staff to report promptly any material increase in pulse rate. In this way patients needing surgery can be detected and so operated on at any hour of the day or night.

When both perforation and haematemesis are present, surgical treatment is desirable if the patient can be made fit enough. But, as others have shown (Slater, 1951), the double diagnosis is hard to make when shock from haemorrhage is severe.

Causes Other than Ulcer

In our series the proportion due to causes other than ulcer (57 of 300 cases) is a little higher than in the large series of Avery Jones (1957). This is partly due to the interest of the professorial surgical unit in portal hypertension, for a few of these cases are admitted as emergencies with haematemesis. Our figures are otherwise too small and the cases too varied to justify further comment.

Seasonal Variations in Hospital Admissions for Haematemesis and Melaena

The first report that peptic ulcers are more likely to perforate in the winter is attributed to Brunner (1903), and this has been amply confirmed by Illingworth, Scott, and Jamieson (1944). The results in our series show that the same rhythm is now clear in the incidence of bleeding from ulcers. This finding is likely to be influenced somewhat by unknown factors, such as a possible increase of old people in Bristol in the winter and their departure during the summer holiday season, but the large variations in numbers in Fig. 6 are unlikely to be due to such factors and probably reflect the aggravation of ulcers in the winter, the causes of which as yet have been only surmised (Illingworth, 1952).

Summary

A total of 300 patients with haematemesis or melaena have been reviewed.

The incidence rose in the older age groups; 33% of the series were 60 years of age or older.

Peptic ulcer or erosion was diagnosed in 81%.

Bleeding did not seem to be more serious in patients who had bled in the past.

The proportion of ulcer patients who had a partial gastrectomy as an emergency for continued bleeding was greater in those over 40 years of age; in men between 40 and 59 the rate of this emergency operation was 23%.

Among the 259 admissions for bleeding ulcer there were 14 deaths (5.4%).

Four patients with ulcer died from continued haemorrhage, two had been treated medically and two surgically.

Over the age of 60 the major hazard in patients with bleeding ulcers was from their associated diseases.

In this series there were about twice as many admissions in the winter as in the summer.

All members of the consulting staff of the Bristol Royal Infirmary allowed me to report their cases. Mr. A. E. J. Turner, records officer, and his staff in the United Bristol Hospitals, undertook the heavy task of collecting together the records with the aid of the diagnostic index. Dr. P. C. Farrant, Dr. K. R. Gough, and Dr. H. de V. Heese collaborated in preparing punch-cards; I owe them my grateful thanks. I also thank Professor C. Bruce Perry for his encouragement and advice.

REFERENCES

- Brunner, F. (1903). *Dtsch. Z. Chir.*, **69**, 101.
- Doll, R., Jones, F. A., and Buckatzsch, M. M. (1951). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 276.
- Fraenkel, G. J., and Truelove, S. C. (1955). *Brit. med. J.*, **1**, 999.
- Gunz, F. W., Gebbie, I. D., and Dick, R. C. S. (1954). *Ibid.*, **1**, 950.

- Illingworth, C. F. W. (1952). In *Modern Trends in Gastroenterology*, edited by F. Avery Jones. Butterworth, London.
- Scott, L. D. W., and Jamieson, R. A. (1944). *Brit. med. J.*, **2**, 617, 655.
- Jones, F. A. (1947). *Ibid.*, **2**, 441, 477.
- (1955). *Gastroenterology*, **30**, 166.
- (1957). *Brit. med. J.*, **1**, 719, 786.
- and Pollak, H. (1945). *Ibid.*, **1**, 797.
- Lewin, D. C., and Truelove, S. (1949). *Ibid.*, **1**, 383.
- Marriott, H. L., and Kekwick, A. (1935). *Lancet*, **1**, 977.
- Meulengracht, E. (1935). *Ibid.*, **2**, 1220.
- Ogilvie, A. G., Cardoe, N., and Bentley, F. H. (1952). *Brit. med. J.*, **2**, 304.
- Slater, N. S. (1951). *Ibid.*, **2**, 1257.

RELIEF OF POST-OPERATIVE PAIN

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Relief of pain following major surgery is necessary for two main reasons: (1) the patient's general comfort; and (2) to enable limb, trunk, and breathing exercises designed to prevent post-operative complications, particularly thrombosis and embolism, to be carried out satisfactorily. In an endeavour to find the best available means of relieving post-operative pain a study was made of three recently introduced analgesics—dihydrocodeine, dipipanone, and dextromoramide (R 875)—to determine if these offered any advantage over conventional analgesics, such as morphine.

Chemistry and Pharmacology

Dihydrocodeine, a close chemical analogue of morphine, was first reported to be a potent analgesic in the experimental animal by Eddy and Small (1934). Gravenstein *et al.* (1956) showed that 30 mg. of dihydrocodeine was approximately equianalgesic with 10 mg. of morphine, with a slightly shorter duration of action, but with substantially fewer side-effects. These workers found that increasing the dose from 30 to 45 mg. did not appreciably enhance the analgesic effect.

Dipipanone is related chemically to methadone, and its analgesic properties were first described by Ofner *et al.* (1950). Cahal (1957) showed that a dose of 25 mg. raised the pain threshold in man to the same extent as did 10 mg. of morphine. Its use in doses of this order for the relief of pain due to acute and chronic medical conditions and in post-operative pain was reported by Gillhespy *et al.* (1956) and its use as an analgesic in labour by Coleman *et al.* (1957). In these studies adequate relief of pain was obtained in about 95% of cases, with an incidence of side-effects of less than 5%.

Dextromoramide, chemically a new type of analgesic, was synthesized and its analgesic properties first described by Janssen and Jageneau (1957). Although weight for weight twenty times more potent than morphine in the experimental animal, its ability to raise the pain threshold in man was found by Cahal (1958)

to be approximately the same. Its use in the treatment of pain in doses up to 10 mg. was reported by Soupault *et al.* (1957) and by David and Deligné (1957).

The structural formulae of the three analgesics are as follows:

Method and Materials

As papaveretum, the post-operative analgesic already in use by us for a number of years, was reliable, and as its analgesic properties could be attributed to its content of morphine, it was used in preference to morphine itself as the standard with which to compare the other drugs. It was thought that the safest form of trial consistent with a fair comparison of these four potentially dangerous drugs was to treat similar series of post-operative patients with each of them in random order. The number of patients treated, the nature of the operations performed, and the order in which the analgesics were given are shown in Table I. The four

TABLE I.—Details of Cases Treated

Order	Analgesic	Major Gynaecological Surgery	Lower Segment Caesarean Section	Total Cases
1	Papaveretum 20 mg. ..	100	25	125
2	Dipipanone 25 mg. ..	100	25	125
3	Dihydrocodeine 50 mg. ..	40	20	60
4	Dextromoramide 10 mg. ..	55	25	80
	Total ..	295	95	390

series of cases treated were similar with respect to the patients' mean age and weight, the type and duration of operation, the surgical techniques used, and pre-operative and post-operative care.

The dose level chosen for each drug was that which on the basis of the available clinico-pharmacological data would be expected to give a good level of analgesia with minimal side-effects. These were: papaveretum 20 mg., dipipanone 25 mg., dihydrocodeine 50 mg., and dextromoramide 10 mg. These doses were approximately equianalgesic with morphine 10 mg. (1/6 gr.) and the drugs were administered subcutaneously every six hours