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CHOICE OF DRUGS IN THE TREATMENT OF DUODENAL ULCER*

BY

A. H. DOUTHWAITE, M.D., F.R.C.P.

Physician to Guy's Hospital

Much has been written during the last quarter of a century on dietetic control of duodenal ulceration, whereas the rational use of drugs has been to a great extent ignored. It is on the latter therapeutic measure that I present the following observations.

Belladonna

The use of belladonna in the treatment of duodenal ulcer has been practised widely for 25 years. Experiments on animals, and later on human beings, led to the belief that the drug caused a considerable reduction in acid output by virtue of a paralysing action on the vagal nerve-endings. Thus Bennett (1922) emphasized the value in this respect of washing the stomach with a dilute solution of atropine before meals. It soon became standard practice to give belladonna or atropine, usually 5 minims (0.3 ml.) of tincture of belladonna before alternate two-hourly feeds (Ryle, 1923) and 1/100 gr. (0.65 mg.) of atropine sulphate hypodermically at night. Ryle stated that belladonna given in this way would cause dry mouth, relaxation of the pylorus and thus reflux of duodenal contents, and modification of the gastric acidity more than that produced by alkali. Schick (1910) declared that its chief value lay in overcoming pylorospasm, and Crohn (1918) refers to the transient and poor effects of atropine on gastric acidity.

No serious criticism of the use of belladonna as an acid depressant arose until in 1938 Davidson and Nicol communicated to a meeting of the Gastro-Enterological Club the results of experiments which showed that even toxic doses of atropine had no constant or marked influence on gastric acidity. Later Nicol (1939) published a paper reiterating that atropine failed to influence gastric secretion and that its value lay in its antispasmodic action.

If belladonna has in fact any action in reducing gastric secretion it can only be by virtue of its paralysing the vagal terminations. It follows, therefore, that only reflex secretion would be abolished, whereas the more important and lasting humoral secretion would be untouched. On theoretical grounds one would expect some diminution in acid output to be produced by belladonna, the degree of change being influenced by the character of the food—appetizing or monotonous—the personality of the subject, and the period of time following ingestion of food. It would be inconceivable that a therapeutically effective reduction of acidity could be produced by belladonna in any dosage.

In order to confirm Nicol's work I investigated the effect of *l*-hyoscyamine on the test-meal curves of 25 patients with hyperchlorhydria and duodenal ulcer. It will be remembered that the action of belladonna is largely due to atropine, and that atropine is racemic hyoscyamine. Furthermore, the peripheral effect of atropine is almost entirely due to its *l*-hyoscyamine component. As it is this action which concerns us, and as the central stimulant effect of both *d*- and *l*-hyoscyamine is unwanted, the latter drug was clearly one of choice. Hyoscyamine sulphate, 1/80 gr. (0.8 mg.), was given by mouth night and morning for three days. On the fourth day, an hour after the morning dose had been taken, the test-meal was given. It will be appreciated that this is high dosage, equivalent in alkaloid value to 36 min. (2.1 ml.) of tr. belladonnae per dose. Within 36 hours it produced persistent dryness of the mouth, thirst, and dilatation of the pupils. Duodenal ulcer pain, if previously present, disappeared as soon as these signs were manifest, yet it will be seen from Figs. 1a, 1b, 2a, and 2b that the effect on acidity was so slight that it is highly improbable that it would have influenced the pain. Although in a few instances the depression of acidity was more than that shown in these graphs, in no case was it great or prolonged.

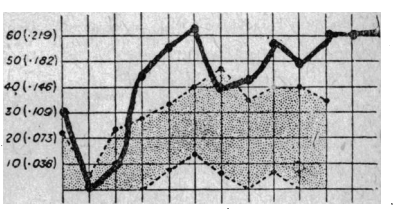

FIG. 1a.—Case of duodenal ulcer. Curve of free HCl during gruel test-meal.

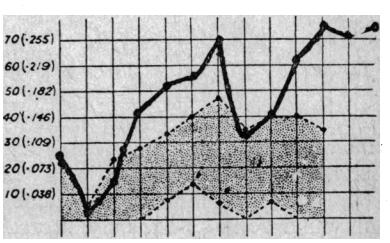

FIG. 1b.—Curve from same patient as Fig. 1a taking hyoscyamine.

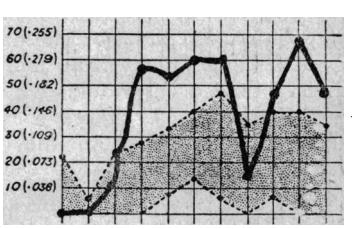

FIG. 2a.—Further case of duodenal ulcer. Gruel test-meal.

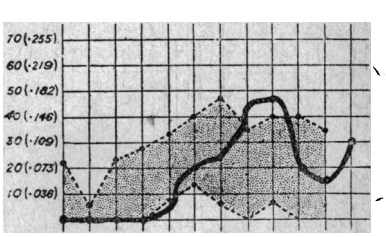

FIG. 2b.—The same as Fig. 2a during hyoscyamine treatment.

If, then, it be agreed that the effect of belladonna on gastric acidity can be disregarded, why is it that it does

* Based on a communication to the Brighton and Sussex Medico-Chirurgical Society on April 3.

in fact relieve pain? Of such action there can be no question provided that adequate quantities be given. No benefit is derived from belladonna unless persistent dryness of the mouth is produced by it. The customary dosage is therefore useless. In practice it will be found that 30 min. (1.8 ml.) of the tincture of belladonna, 1/100 gr. (0.65 mg.) of atropine sulphate, or 22 min. (1.3 ml.) of liquid extract of hyoscyamus given four-hourly will be effective. Yet more efficacious is 1/120 gr. (0.54 mg.) of *l*-hyoscyamine twice daily (Douthwaite, 1939).

It is well known that the belladonna alkaloids have a pronounced effect on the motility of the gastro-intestinal tract, especially in the direction of quelling abnormal contractions. It is also usual to note excessive gastric peristalsis, often combined with pyloric spasm, in patients suffering from duodenal ulcer. Furthermore, rapid emptying of the stomach is common not only during the active phase but also during periods when healing of the ulcer seems to be established. Numerous observers have noted how this hypermotility is abolished by full doses of atropine. It can be demonstrated radiographically, and was noted by Wolf and Wolff (1943) in their experiments on a patient (Tom) with a gastric fistula. They showed, furthermore, that atropine resulted in a great prolongation of emptying time.

If it can be accepted that the pain of duodenal ulcer is due to abnormal contractions of muscle fibres in the stomach or duodenum, or both, the benefit conferred by belladonna can be understood. There are two schools of thought in regard to the pain-producing factor: the one favouring muscular contractions and increased tonus, resting on the observations of Bolton (1928), Christensen (1931), Hurst (1911), Ryle (1926), and Poulton (1928); the other stressing the importance of acidity, based on the work of Palmer (1926), and recently of Bonney and Pickering (1946). The evidence derived from careful clinical experiments by the latter school certainly presents convincing grounds for the belief that a certain level of acidity, varying from case to case, will, if reached, be directly responsible for ulcer pain. This does not, however, exclude the possibility that the muscular contractions may also cause pain or, in fact, may be the usual excitant of pain production. An argument often put forward is that if an intragastric balloon fails to record a rise of tension coincident with pain, increased muscular tonus cannot be incriminated. Such a conclusion is not justified. Only if an increase of gastric tonus as a whole should occur would one expect it to be registrable manometrically. Localized spasm could not possibly influence the tension within the balloon, yet it might well give rise to pain.

The "acid hypothesis" fails to explain certain common features of pain in uncomplicated duodenal ulcer—namely: (1) Its occurrence at 2–3 a.m. and its spontaneous subsidence even if no food or alkali is taken. The chart of gastric acidity (Fig. 3) taken during sleep shows it to be lower at 2 a.m., which was the hour when pain usually wakened this patient. (2) Its spontaneous subsidence before meals if the meal is postponed. (3) Its lessening or disappearance within half an hour of lying down. (4) Its relief from the application of heat to the abdomen. This is known to inhibit gastric and intestinal peristalsis (Bisgard *et al.*, 1942). (5) Its rapid relief by CO_2—producing antacids, whose effect on acidity is transient as compared with the non-gas-producing antacids such as trisilicate. (6) The invariable relief afforded by full doses of belladonna alkaloids.

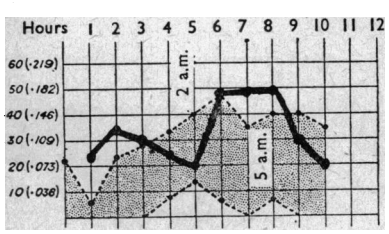

FIG. 3.—Duodenal ulcer. Free HCl curve during night. Samples removed hourly.

It is reasonable also to assume that the pain of gastric and duodenal ulcer has the same mechanism of production; yet in the former case gastric acidity is usually within normal limits and there may, in fact, be no free hydrochloric acid throughout digestion.

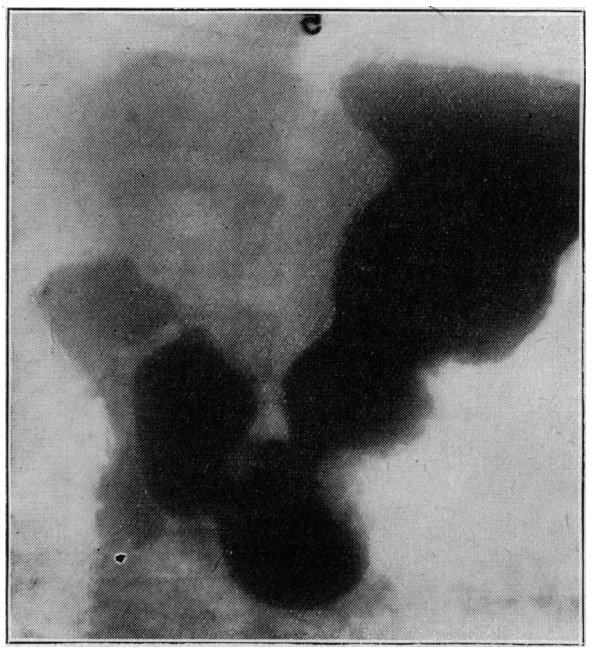

FIG. 4.—Chronic duodenal ulcer. Note hypertonicity and pronounced peristalsis after four weeks' milk-drip.

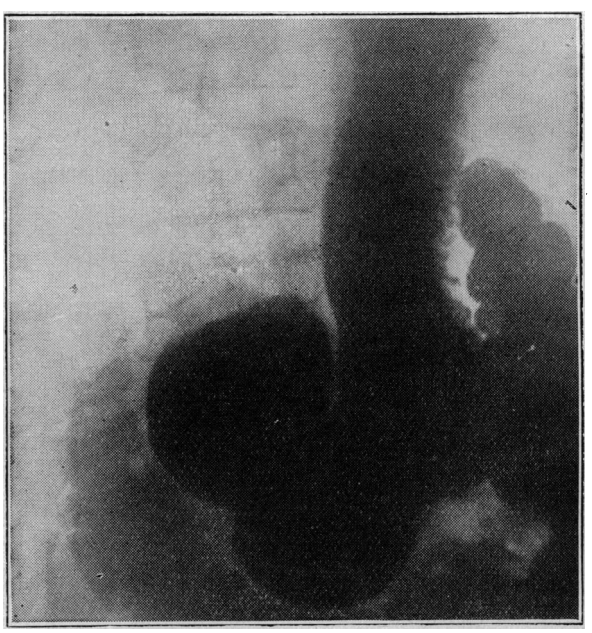

FIG. 5.—The same as Fig. 4, one day later, an hour after hyoscyamine sulphate, gr. 1/80 (0.8 mg.).

Finally, a positive argument in favour of the muscular tension theory is afforded by radiographic observations. The radiographs (Figs. 4 and 5) of the stomach of a sufferer from duodenal ulcer were obtained within 24 hours of each other. Continuous pain was being experienced while

taking Fig. 4, in which a series of peristaltic waves are seen. In Fig. 5 gastric tone and motility are strikingly lessened as the result of 1/80 gr. (0.8 mg.) of hyoscyamine sulphate. The patient was entirely free from pain. Numerous observations have shown the same sequence of events. It follows from this that the operation of vagotomy for duodenal ulcer is wholly unjustifiable. Belladonna can achieve all the good results claimed for such surgery without the danger and permanent mutilation it entails. It is probable that two factors produce pain in peptic ulcer—abnormal muscular contractions, and a chemical stimulus provided by hydrochloric acid. The justification for the use of belladonna is thus established. We have now to consider the control of acidity.

Antacids

No matter what views are held on the mechanism of peptic ulcer pain production, it is common ground that free hydrochloric acid is of great importance in preventing the healing of the ulcer. It is reasonable, therefore, to seek to neutralize this acid so long as an ulcer is present. Once healing has been secured the need is far less, if indeed it exists at all. It should be noted here that Ryle and Bennett (1937), from a follow-up of 100 students subjected to test-meal analysis in 1921, concluded that there was no association between degrees of gastric acidity and the development of dyspeptic troubles.

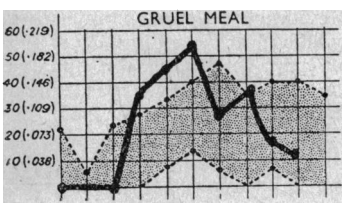

FIG. 6a.

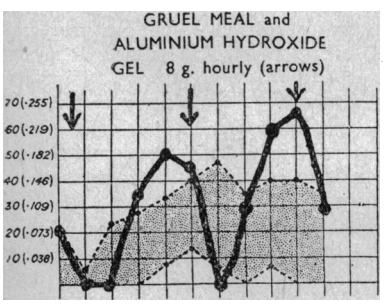

FIG. 6b.

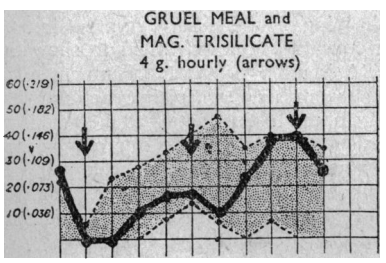

FIG. 6c.

FIGS. 6a, 6b, and 6c.—Free HCl curve showing the transient effect of aluminium hydroxide and magnesium trisilicate.

In point of fact all the drugs commonly used to neutralize gastric hydrochloric acid have such a transient action as to be valueless. The fleeting action of sodium bicarbonate, calcium and magnesium carbonate, and tribasic phosphates is too well known to require further emphasis. Experiments carried out by E. B. French and myself on patients with peptic ulcer (Douthwaite, 1939) showed, furthermore, that aluminium hydroxide gel and magnesium trisilicate when given hourly failed to neutralize hydrochloric acid for more than a quarter of an hour. The former when given by continuous drip, 1 oz. (28 ml.) hourly, was likewise ineffective. Figs. 6a, 6b, and 6c illustrate the short action of these substances. It is true that in a long series one meets with instances in which one or other of the antacids appears to have a prolonged action, but it is the effect on the majority which is of importance.

One of the reasons for the transience of antacid action in cases of duodenal ulcer is that the stomach empties so quickly. The same conclusion was reached by Nicol (1939) in respect of the fact that hourly feeds of milk fail to produce neutralization. He also showed that neither hourly nor two-hourly feeds of milk foods, vegetable purée, eggs, and fish, in conjunction with carbonates, would cause lasting depression of gastric acidity; in fact, two-hourly feeds containing more protein are more effective than hourly milk meals.

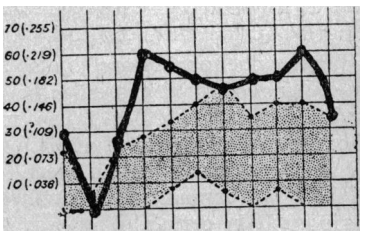

FIG. 7a.—Duodenal ulcer. Gruel test-meal (1/4-hour samples).

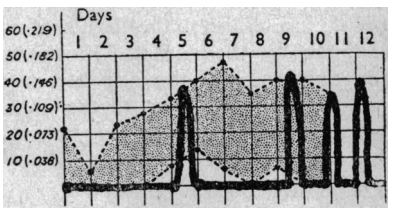

FIG. 7b.—Same case as 7a. Continuous milk-drip, 5 pints (2.84 l.) in 24 hours for eight days; thereafter in daytime only. First rise of acidity due to interruption of drip. The later rises coincided with nights when the drip was suspended.

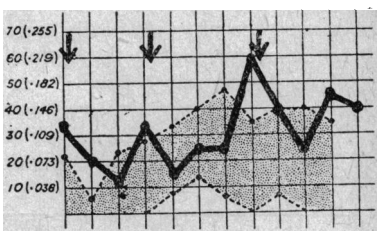

FIG. 7c.—Shows the feeble antacid effect of 5 oz. (142 ml.) of milk given hourly.

The only satisfactory way to neutralize gastric hydrochloric acid for days on end is to give milk by drip-feed through a Ryle's tube passed into the stomach. Five pints (2.84 l.) given in 24 hours may be completely effective, as is shown in Figs. 7a, 7b, and 7c. The patient is seldom intolerant of this treatment, especially if the tube be passed through the nose. It is withdrawn and cleaned twice a week, and the drip can be discontinued at the end of three to four weeks. When such treatment is impracticable the next-best measure is to give 1/2 oz. (14 ml.) of olive oil (this delays emptying and reduces acid output) and 1/2 oz. (15.5 g.) of magnesium trisilicate in 8 oz. (227 ml.) of milk two-hourly, between two-hourly main feeds. These should consist of porridge, egg, milky foods, bread-and-butter, fruit juices, purée of fruit and vegetable, fish, and chicken. In fact, if chemical irritants—for example, mustard, spices, vinegar, and alcohol—are avoided and if other food is free from gross roughage, all the common foods may be safely taken from the beginning of treatment. If a milk-drip is used, then three meals a day may be given in addition to the milk.

Anxiety

After considering hypermotility and hyperacidity, our third and last problem is the control of anxiety, the effects of which are inimical to healing. This has already been done in part by blocking vagal impulses with hyoscyamine. The choice of a suitable cerebral sedative is not a matter of great difficulty. Phenobarbitone answers the purpose in the majority of cases. It may, however, prove unsuitable by causing skin rashes, fever, giddiness, and incoordination. More commonly it produces intense depression of spirits and disinclination to co-operate in the full treatment of peptic ulcer. Yet again, it may

completely fail to relieve anxiety and restlessness unless given in excessive doses. If 1 gr. (65 mg.) thrice daily fails to produce the desired effect it is wiser to change the drug than to increase the dosage. It should be borne in mind that phenobarbitone is an indifferent hypnotic, and that at night it is usually necessary to give a more potent soporific—for example, "sodium amytal," 3 gr. (0.2 g.).

When phenobarbitone fails a state of mental and muscular relaxation can be achieved by the use of cannabis indica. This drug has fallen into undeserved disrepute because of the danger of addiction, and even more because its preparations are often inert. The former risk is very slight when cannabis is used therapeutically for a limited period. It is certainly far less than that entailed by the use of opium and its derivatives. Taken by a patient resting in bed, and thus removed from any suggestion of conviviality, it produces a languorous state and sense of well-being, without the flights of imagination for which it is taken by the addict. Furthermore, it does not cause constipation, and the appetite is unimpaired. In fact, it may lend enchantment to the dietary.

Extractum cannabis (*B.P.C.*) is the preparation of choice; the tincture has a most unpleasant taste, and its resin is precipitated by the addition of water. The recommended dose of 1 gr. (65 mg.) is too small to be effective. Four times this amount should be given in capsules four times daily. The frequency of administration is adjusted to the result. It will allow of continuous drip-feeding in patients who would otherwise be intolerant of it. It is seldom necessary to give the drug for longer than two weeks, and a supply should never be left in the patient's charge. I have used the physiologically tested extract and have found it to be active, but it is as well to procure only a small stock at a time and to keep it at a low temperature—10° C. The effectiveness of the drug in inducing, presumably by central action, relaxation of the stomach is well illustrated by Figs. 8a and 8b. Symptomatically this patient suffered

FIG. 8a.—Chronic duodenal ulcer with clinical signs of stenosis. This is masked in the radiograph because of powerful peristalsis.

from pyloric obstruction, yet the emptying rate, determined radiologically, was rapid. The second radiograph (Fig. 8b), taken after treatment with cannabis at the same time, after a barium meal, shows that the rapid emptying was the result of hyperperistalsis and that true obstruction was present. This was confirmed at operation.

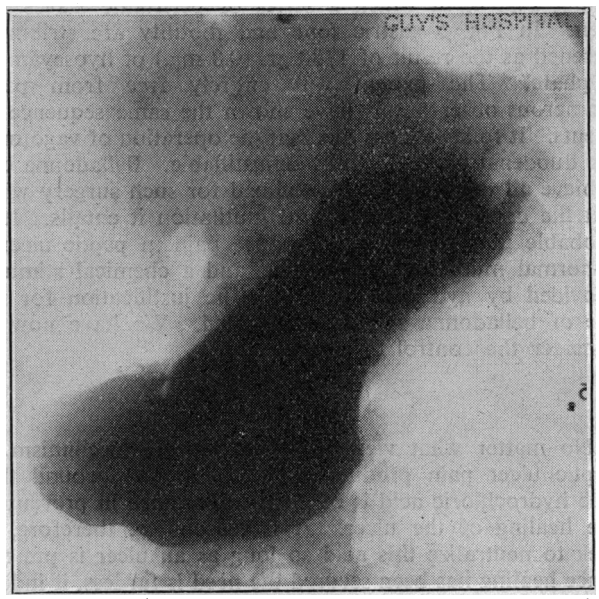

FIG. 8b.—Same case as 8a when taking 4 gr. (114 ml.) of ext. cannabis four times daily. Stomach relaxed; stenosis revealed.

Harmful Drugs

In conclusion a brief reference to chemical substances which may aggravate symptoms of ulcer should be made.

Tobacco.—Experimental evidence favours harmlessness of smoking to patients with chronic ulcer. Neither rate of emptying of the stomach nor acidity can be shown to be appreciably affected. As against this it is a spontaneous observation of countless sufferers from duodenal ulcer that the pain, in the active phase of the disease, will always be produced or, if present, aggravated by the smoking of a single cigarette. Again, on inquiring into change of habits preceding a relapse, how often does one find that the only prophylactic measure which has lapsed has been abstinence from tobacco. It may well be that direct irritation of the gastric and duodenal mucosa is set up by pyridine, furfural, and acrolein, which are present in tobacco smoke and which are swallowed in saliva. I have no doubt that smoking should be limited—a pipe after breakfast and another after dinner—throughout the life of the patient.

Mustard, vinegar, curry, and strong alcoholic drinks and the like are chemical irritants and should clearly be avoided. For the same reason chloral hydrate is an unsuitable hypnotic for the sufferer from peptic ulcer.

Aspirin.—The possibility that aspirin might act as an irritant to the gastric mucosa, and thus cause melaena, was raised by me some years ago (Douthwaite, 1938). Later, Lintott and I (Douthwaite and Lintott, 1938) carried out gastroscopic observations to determine whether this was in fact the case. We were able to show that an inflammatory reaction developed around particles of aspirin lying on the lesser curvature in 80% of subjects. The greater-curvature mucosa failed to show this change, no doubt because it is more protected by mucus. The failure of Wolf and Wolff to produce an aspirin reaction in the mucosa of Tom may be attributed to this fact or to their subject's belonging to the 20% resistant group. Since our communication on this matter confirmatory evidence has been plentiful. We were able to show that calcium aspirin in solution was entirely free from harmful effects. When the drug is indicated it is this form which should be prescribed.

After-treatment

Drugs have but little place in therapy once the ulcer has healed. That is to say, after two months of thorough treatment it is seldom necessary to add drugs to the advice we give for the regulation of the patient's habits. Adequate time for meals, thorough mastication, extra food between meals, avoidance of chemical irritants, nine hours in bed nightly, and the refusal to attend to the telephone during

meals or at night are far more important than dietary schemes, which are unnecessary, and drugs.

We know that the high gastric acidity persists and that the exaggerated peristalsis often subsides if the patient is free from worry and stress. The first sign that it is returning is usually that of vague discomfort before food or of waking in the night for no apparent reason. I believe that this gastric unrest precedes duodenal ulceration. If I am right its prompt control should prevent the relapses which hitherto have been a reproach to our therapeutics. Therefore, when such early symptoms are noticed, or again during periods of mental fatigue, worry, and stress, the administration of belladonna alkaloids should be resumed and be continued until the patient has been symptomless for a week. It is especially the night dose which is of value. Alkaline or antacid preparations have no place in therapeutics at this stage: they mask symptoms and encourage relapse.

Summary and Conclusions

The value of belladonna and its correct administration in treatment of duodenal ulcer are described. The relationship of ulcer pain to acidity and hypermotility is discussed. The use of antacids is considered. The value of phenobarbitone and cannabis indica is described. Reference is made to certain substances in common use which aggravate peptic ulceration.

Belladonna reduces gastric and duodenal spasm and the emptying rate of the stomach. It does not affect acidity. To be effective the dose must be large enough to cause persistent dryness of the mouth. The operation of vagotomy is unjustifiable. Alkalis and other antacids have such a transient and variable effect on gastric acidity that they might well be discarded as of little value. If given they should be combined with the administration of olive oil. Their danger lies in the masking of symptoms while the disease progresses. Continuous milk-drip-feeding often completely neutralizes free hydrochloric acid in the stomach. Cannabis indica is a valuable sedative for use in the acute phase.

The cannabis indica used in these experiments was kindly supplied by British Drug Houses, Ltd.

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Dr. Simon Flexner, who was born in 1863 and died in 1946, is commemorated in a pamphlet issued by the Rockefeller Institute for Medical Research, printing speeches delivered on June 12, 1946, at a memorial meeting. In 1902 the Board of Directors requested Dr. Flexner to state his views on the establishment of a research institute, and in 1903 he went to New York to take charge of the Rockefeller Institute's pathological laboratories, becoming Director of the Institute in the same year. One of the speakers quotes from a speech he made in 1933: "There are no closed compartments in nature into which man, animals, and plants can be separately placed. All are related organically and, as we may say, united physiologically and pathologically. . . . If, therefore, we would learn, and through learning grow more powerful and effective to prevent and cure disease, to lengthen life and to increase happiness through security in all its various forms, then we should endeavour to advance in biological knowledge, which alone can free us still further from the evils of disease."

BORNHOLM DISEASE IN THE TROPICS

BY

W. M. JAMIESON, M.D., D.P.H.

Formerly Wing Commander, Medical Specialist, R.A.F.V.R.

AND

D. M. PRINSLEY, M.B., B.S.

Formerly Squadron Leader, Medical Officer, R.A.F.V.R.

An outbreak of Bornholm disease occurred at Aden in the late hot season of 1946. Between Aug. 17 and Oct. 25 we saw 35 cases. This malady has at various times been reported from Northern Europe, U.S.A., Britain, Southern Australia, and more recently from Egypt. So far as we are aware only one previous outbreak of the disease has been reported in the Tropics (McDaniel, 1944), although conversation with Service colleagues has indicated that it is not unknown in parts of tropical India and in Singapore. Aden, although a busy port of call on the East–West routes by sea and air, is nevertheless a relatively small and well-defined community, or rather collection of communities, and eminently suitable for studying an epidemic. All our cases were treated in the R.A.F. hospital, with the exception of two admitted to neighbouring sick quarters, two seen at their home (family of an R.A.F. officer), and one Arab taxi-driver who attended as an out-patient.

The same basic syndrome, with minor variations, has been described under many titles—"epidemic muscular rheumatism," "devil's grip," "epidemic myalgia," "Bornholm disease," "epidemic myositis," "epidemic pleurodynia," and "acute benign dry pleurisy." The condition is infective in origin and almost certainly primarily a lesion of the diaphragm, the exact nature of which is not clear. In view of this we have preferred to retain, for the present at least, the somewhat meaningless title first given to the syndrome by Sylvest (1934)—namely, "Bornholm disease."

With the exception of one case (the Arab taxi-driver) the outbreak was confined to personnel of the Services and their families. The age incidence, therefore, was such as might be expected from any condition affecting the Forces (Table 1). The incidence among officers and other ranks was: officers, 6; officers' families, 3; other ranks, 24; other ranks' families, 2. The ratio of British officers to other ranks in Aden is approximately 1 : 13. The relatively high incidence of the disease found in officers is thus in accordance with the Egyptian experience of Scadding (1946), who noted a "more common incidence among officers than among other ranks."

TABLE I.—*Age and Sex Incidence*

Age:	0–10	10–15	15–20	20–25	25–30	30–35	35–40	40–45	45+	Total
Males ..	0	1	6	16	3	2	0	2	0	30
Females	0	1	0	1	1	1	1	0	0	5
Total	0	2	6	17	4	3	1	2	0	35

Clinical Features

Mode of Onset.—The onset was usually abrupt, with pain, headache, and some degree of fever as the most constant features. Only five cases suffered from upper respiratory tract catarrh, for periods varying between a few days and three weeks, before the onset of classical symptoms. Two cases had prodromal colic and diarrhoea, while a further two complained of lumbar backache for a few days previous to the attack. It is difficult to assess the significance of these various prodromata, since the commonest ailments seen in Aden are probably upper respiratory tract