PILOCARPINE AS AN ANTAGONIST TO THE UNDESIRE EFFECTS OF GANGLION-BLOCKING AGENTS IN THE TREATMENT OF HYPERTENSION

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A disadvantage in the use of ganglion-blocking agents for the reduction of hypertension is that they block conduction not only through sympathetic but also through parasympathetic ganglia. The desired lowering of blood pressure is due to the action on the former, the undesirable effects mainly to the action on the latter. It would be a clear advantage if the effects on parasympathetic ganglia could be neutralized.

It seemed to us that this ought to be readily done by the use of pilocarpine. This drug acts peripherally on the post-ganglionic terminals, and its action should not be prevented by simultaneous paralysis of the pre-ganglionic fibres to the ganglia. In medicinal doses it has no action on the post-ganglionic sympathetic terminals, so that it should not diminish the hypotensive action for which the ganglion-blocking drug is given. A preliminary trial on a suitable patient has confirmed this anticipation.

Case Report

The patient, a woman aged 45, had been treated since March, 1953, first with hexamethonium bromide intramuscularly, and later, for the past five months, with pentolinium tartrate ("ansolysen") orally. Both treatments gave very satisfactory results in reducing the hypertension and concomitant symptoms, but in doses sufficient to maintain an adequate reduction of blood pressure the side-effects were distressing. These were of the usual type: dryness of the mouth, leading to interference with speaking and swallowing; constipation and loss of appetite; dryness of the eyes and loss of accommodation; and, especially with hexamethonium, difficulty with micturition.

The patient was given orally a tablet containing 1/10 gr. (6.5 mg.) of pilocarpine nitrate. Within half an hour she reported that "instead of my mouth being parched, I can do nothing but spit." As the salivation was unnecessarily copious, half a tablet was next given. This produced slight moistening of the mouth, but not enough. A dose of about 1/13 gr. (5 mg.) (three-quarters of a tablet) has subsequently proved adequate for keeping the mouth in a satisfactory state of moistness. On this dosage the side-effects of pentolinium tartrate have largely disappeared. Certainly the dryness of the mouth and eyes is relieved, and appetite and digestion have improved. This has made a great difference to the patient's sense of well-being, which has been maintained for five weeks on a dose of pilocarpine of 1/10 to 1/13 gr. (6.5 to 5 mg.), during which time she has led a normally active life. The dryness of the mouth, an effect easily appreciated, disappears regularly within half an hour of swallowing the pilocarpine and returns in six to ten hours, depending on the dose. The patient has also remarked, without questioning, that the constipation has been less.

Comment

Pilocarpine, by stimulating all parasympathetic nerve-endings (or by some action equivalent to this), has a wide-

spread action on involuntary muscle and on secreting glands, and is a potential antagonist to all the effects which result from paralysis of parasympathetic ganglia. It would presumably have this effect in the case of any ganglion-blocking agent. In smaller doses it acts more on glands than on muscle, and might therefore be expected to antagonize the effects of ganglion-blocking agents on secretions more readily than those on muscle.

The loss of tone and of contractions of the alimentary tract which often occurs with ganglion-blocking agents is no doubt mainly due to blockage of the motor impulses to the muscle, but the diminution of salivary, gastric, and intestinal secretions can hardly fail to aggravate the constipating effect. Some improvement of this condition may therefore occur even if the dosage of pilocarpine is only high enough to act on secretions. In larger doses it powerfully stimulates intestinal muscle. It has also some action on ganglia, but this could hardly occur with medicinal doses. To what extent it could be safely used to antagonize the various muscular and glandular effects resulting from parasympathetic ganglion-block would require detailed exploration. It would be a question not only of dosage but probably to some extent also of individual variations in quantitative response. Fortunately, medicinal overdosage with pilocarpine can be readily antagonized with atropine should need arise.

We have not encountered in the literature any mention of pilocarpine having been tried for the purpose we have indicated, other than a passing reference by Smirk (1953). Our object in submitting this note is to suggest that it may prove of value for counteracting some at least of the undesirable side-effects which often mar the desired depressor effects of ganglion-blocking agents.

REFERENCE

Smirk, F. H. (1953). *N.Z. med. J.*, 52, 325.

THE ROLE OF SMOKING IN BRONCHITIS

BY

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Many factors which are responsible for the development or aggravation of bronchitis, such as climate, atmospheric impurities, hereditary predisposition (Oswald *et al.*, 1953), and infection (Stuart-Harris *et al.*, 1953), are difficult to control or eradicate. It is important, therefore, to assess the role of factors, such as smoking, which are more easily controlled. This investigation was undertaken to assess the incidence of bronchitis in a group of smokers compared with a similar group of controls who were non-smokers.

The patients studied consisted of a consecutive group of 422 males who were admitted to the Middlesex Hospital during the period from September, 1950, to September, 1952, for elective repair of inguinal hernia or a partial gastrectomy for chronic peptic ulcer. There were 310 smokers and 112 non-smokers.

Method

I examined each patient before the operation, and a postero-anterior radiograph of the chest was taken. The age, the place of residence, and a past history of diseases likely to predispose to the development of bronchitis were noted. Table I shows the distribution of these factors in the groups.

TABLE I.—Comparison of Groups of Smokers and Non-smokers

	No.	Average Age (Years)	Place of Residence			Past History			
			Urban	Sub-urban	Rural	Hay-fever	Asthma	Nasal Catarrh	Pneumonia
Smokers	310	47	152	138	20	12	5	31	33
		S.D. 12	49.0%	44.5%	6.5%	3.9%	1.6%	10.0%	10.6%
Non-smokers	112	48	51	55	6	3	3	10	12
		S.D. 12	45.5%	49.1%	5.4%	2.7%	2.7%	8.9%	10.7%

The patients' smoking habits were classified as follows: heavy, 20 or more cigarettes a day; moderate, 10–19 cigarettes a day; light, fewer than 10 cigarettes a day.

There were fewer than 10 pipe smokers. In these, 1 oz. (28 g.) of tobacco was taken as roughly equivalent to 30 cigarettes.

Patients were classified as non-smokers if they had never smoked, or if they had given up smoking for a year or more before admission. Ten patients had given up smoking more recently, and these were excluded from the series.

Diagnosis of Bronchitis

This was considered under three headings: a history of bronchitis, clinical evidence of bronchitis, and radiological evidence of bronchitis. It is well known that the principal symptom of bronchitis is cough, productive of a variable amount of expectoration. The common history is that the symptoms start in the winter, often following a cold. In succeeding winters the duration of the cough after each attack progressively increases. This phase gradually gives place to a constant cough and expectoration with winter exacerbations (Scadding, 1952). Quite marked winter bronchitis is quiescent in the summer, when some of these cases were interviewed. Thus if the patient admitted to a productive cough which had lasted a fortnight or more during two preceding winters he was deemed to have a positive history of bronchitis. A dry cough, due to pharyngitis, for example, was not considered such a reliable indication of bronchitis, and patients with a dry cough only were not included.

Bronchitis was diagnosed clinically when rhonchi or numerous coarse rales were found on examination of the chest. Minimal fine rales at the lung bases which cleared readily on coughing were not considered to justify a diagnosis of bronchitis, as this is a common finding in patients who are in bed.

The radiological changes of bronchitis are not distinctive. Bronchitic changes were considered to be present radiologically when there was an increase in the density of the bronchovascular markings in the outer two-thirds of the lung fields. These changes were seen only in the more severe cases of bronchitis, and were usually associated with some degree of emphysema. No cases of pulmonary congestion due to heart disease were seen in this series.

Of the 422 patients, 47.4% gave a positive history of bronchitis, 28.4% showed clinical evidence of bronchitis, and radiological changes were present in 14.2%.

Results

In Table II the incidence of bronchitis in the group of smokers is compared with that in the non-smoker group. It can be seen that the incidence was definitely higher in the smokers than in the non-smokers. The incidence

TABLE II.—Incidence of Bronchitis in Smokers and Non-smokers

	No.	History of Bronchitis	Clinical Evidence of Bronchitis	Radiological Evidence of Bronchitis
Smokers	310	166 (53.5%)	100 (32.2%)	53 (17.1%)
Non-smokers	112	34 (30.4%)	20 (17.9%)	7 (6.2%)
Difference		23.1% (S.E. 5.19)	14.3% (S.E. 4.49)	10.9% (S.E. 3.13)

of bronchitis in the groups, moreover, differed by more than twice the standard error, so that these differences are unlikely to have arisen by chance.

The main factors other than smoking which are likely to predispose to a history of bronchitis are satisfactorily distributed between the groups (Table I), so that the higher incidence of bronchitis in the smokers may be reasonably considered to be associated with smoking.

In Table III the incidence of bronchitis is compared with the amount smoked. It is apparent that the incidence of bronchitis increases markedly with increased smoking.

TABLE III.—Incidence of Bronchitis Compared with Amount Smoked

	No.	History of Bronchitis	Clinical Evidence of Bronchitis	Radiological Evidence of Bronchitis
Heavy smokers	42	31 (73.8%)	29 (69.0%)	16 (38.1%)
Moderate "	127	73 (57.5%)	39 (30.7%)	23 (18.1%)
Light "	141	62 (44.0%)	32 (22.7%)	14 (9.9%)
		$\chi^2 = 12.91$ $n = 2$ $P < 0.01$	$\chi^2 = 32.05$ $n = 2$ $P < 0.01$	$\chi^2 = 18.27$ $n = 2$ $P < 0.01$

This trend is very unlikely to have arisen by chance ($P < 0.01$).

Older people are more likely to have a history of bronchitis than younger ones, but this is unlikely to be the reason for this trend as the average age for the heavy smokers was 45.4 years, for the moderate smokers 48.0 years, and for the light smokers 47.6 years.

Discussion

In this series of adult male patients, bronchitis, based on clinical and radiological findings, was significantly commoner in smokers than in non-smokers. The incidence of bronchitis, moreover, increased significantly with the amount smoked.

Of 1,000 patients with chronic bronchitis studied by Oswald and his colleagues at the Brompton Hospital, only 5% were non-smokers. They also found that there were appreciably fewer non-smokers among 300 patients with bronchitis than among a comparable control group without bronchitis. Moreover, these authors found that half the smokers felt that smoking aggravated their bronchitis, and that a large number had abandoned the habit with benefit.

In a disease with so many aetiological factors as bronchitis, smoking is obviously unlikely to be the only factor concerned. The incidence of a history of bronchitis, for example, was as high as 30% in the non-smoking group in this series, and 26% of the heavy smokers gave no history of bronchitis. Nevertheless, these results suggest that smoking is of considerable importance in the aggravation of bronchitis, and it follows that in the management of these cases, in addition to the usual measures, they should be encouraged to give up smoking.

Summary

In a group of 422 males there were 310 smokers and 112 non-smokers.

The incidence of bronchitis was significantly higher in the smokers than in the non-smokers.

The incidence of bronchitis increased with the amount smoked.

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REFERENCES

- Oswald, N. C., Harold, J. T., and Martin, W. J. (1953). *Lancet*, 2, 639.
Scadding, J. G. (1952). In *Diseases of the Chest*, vol. 1, edited by Sir Geoffrey Marshall and K. M. A. Perry. Butterworth, London.
Stuart-Harris, C. H., Pownall, M., Scothorne, C. M., and Franks, Z. (1953). *Quart. J. Med.*, 22, 121.