severe cases to produce a cuff-like appearance (Fig. 1). In addition most cases when viewed laterally show the well-known web appearance (Figs. 2 and 3).

For reasons of safety, gastroscopy is not undertaken, though the condition of the gastric mucosa is of great theoretical interest. Gastroscopists should beware of women in this age group, since they may have an undeclared stenosis of this kind.

Follow-up should be directed to securing a permanently normal haemoglobin, and redilatation should the stenosis recur. In the worst cases a surgical or radium menopause may be necessary if oral iron cannot keep the blood normal. Frequent endoscopy to detect early cancerous change is impractical and of doubtful value.

If the anaemia is gross it should be corrected before dilatation. However, no quantity of iron will correct the dysphagia. If in doubt whether to dilate or not it is useful to remember that inability to eat meat is an absolute indication for the procedure.

Prognosis and Causation

Redilatation may be needed as often as every year (Case 2). Repeated courses of iron will be necessary till the menopause occurs. Two of our 16 cases developed carcinoma (Cases 4 and 8). Simpson (1939) reported that 10 of his 18 cases developed carcinoma.

The cause of mucosal atrophy in the upper gastrointestinal tract, the relationship of this to hypochromic anaemia, and the relationship of both to the oesophageal stenosis are quite unknown. Whatever the condition of the gastro-intestinal tract, it seems clear that the dysphagia does not occur unless iron-deficiency anaemia has been present. Despite superficial resemblances there seems to be no relationship to ariboflavinosis. The exclusive incidence in women is sufficiently accounted for by their peculiar liability to menstrual blood-loss anaemia. The incidence of hypochromic anaemia in Northern Ireland is considerable, and is to be attributed to the inadequate nutrition common in middle-aged women in Northern Ireland and to uncorrected menorrhagia. The implications for prophylaxis of post-cricoid carcinoma by improved nutrition and effective treatment of menorrhagia are obvious.

Summary

The clinical diagnosis of Plummer-Vinson disease is described. The dysphagia is due to organic stenosis. Dilatation of the stricture is the essential treatment. Plummer-Vinson disease is a pre-cancerous condition.

We are much indebted to Mr. Kennedy Hunter, Mr. R. S. McCrea, Mr. W. Matthews, and Dr. Martin Beare for the opportunity of studying their patients, and to Mr. D. Mehaffey, A.R.P.S., for the photographs.

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A guide to epileptic colonies, the accommodation they offer, their charges, training, etc., has been published by the British Epilepsy Association (price 1s.). Although only sane epileptics are admitted to the colonies, the standards of subnormality for exclusion vary. The handbook gives details for each colony of the method of admission and administration, conditions for discharge of patients, and the length of the waiting-list. The booklet points out that, while the provision of a permanent sheltered home remains an important function of these colonies, the main object of care is to stabilize the patient sufficiently to permit return to work.

ANTI-SIALOGOGUE AND OTHER EFFECTS OF ATROPINE MUCATE

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Although it is barely 50 years since atropine began to be used to inhibit salivary secretion before the administration of an anaesthetic, this drug has come to be regarded as an essential requirement in these circumstances. Pre-operative administration of atropine is so important that if it has been omitted most anaesthetists would either postpone the operation or administer atropine intravenously.

In big hospitals with long operating lists it is usually impossible to estimate the correct time for the administration of atropine. Any preparation of this drug whose effect would be so prolonged that accurate timing was unnecessary would be an important and welcome innovation. We regarded it as of some clinical importance, therefore, to investigate further the claim made by Asquith and Thomas (1948) that hypodermic injections of atropine mucate ("hyperduric atropine") lead to a more prolonged inhibition of salivary and mucus secretion than do the more commonly used atropine sulphate or tartrate.

Asquith and Thomas in their paper relied on clinical observation and apparently used no criterion for assessing the anti-sialogogue effect, other than their own or their patients' opinion. We decided to use a more objective and quantitative method of estimation, in volunteers in whom many environmental factors could be controlled.

The only published method we found for studying salivary secretion was that of Lashley (1916), and its modification by Richter and Wada (1923). In this method the parotid duct is cannulated and the saliva allowed to flow through a long glass tube. The passage of a bubble of air introduced into the stream of saliva is timed over a measured distance. This method was deemed unsuitable for an experiment requiring frequent observations over a period of perhaps six hours. We considered and discarded the suitability of other methods of cannulation of one or more salivary ducts. Electrical measurement of the wetness of the mucosa of the mouth was unsatisfactory, and so was weighing pledgets of wool allowed to soak saliva for a fixed time.

Method

We finally devised the following method for measuring the salivary activity at any particular moment. The subject swallows repeatedly, to get rid of any saliva present in the mouth. Four drops of lemon juice (a powerful if not a specific stimulus) are then placed on the tongue and allowed to act for 30 seconds. The mouth is then rinsed for 15 seconds with 5 ml. of water, the subject then spitting into a funnel and measuring cylinder. For a further 15 seconds the mouth is emptied by repeatedly spitting into the measur-

ing cylinder. The froth on the collected washings is touched with a glass rod dipped in caprylic alcohol, and the rinsings are measured. This amount minus 5 ml. is the salivary secretion in response to the lemon-juice stimulus. We call this amount the salivary index.

The salivary index was first measured at quarter-hour intervals for about one hour before injection was made. A dose of 1/100 gr. (0.65 mg.) of either atropine mucate or atropine sulphate was then injected subcutaneously over the deltoid muscle in the arm and the index measured every 15–20 minutes until several consecutive readings had returned to the pre-injection range. The pulse was counted each time the salivary index was obtained. Each subject submitted to testing with atropine mucate on one day and to atropine sulphate on another day. Altogether nine subjects were tested, and a series of "paired" results were obtained.

Subjective Sensations.—All the subjects felt dry at the height of the action of the drugs. Beyond that point their opinion was unreliable, being often at variance with the salivary index. Several of them thought that salivary secretion was free when measurement showed that it was still very depressed. A few of the subjects felt drowsy when the action of both types of atropine was at its maximum. Two of them actually fell asleep for a short period. This is perhaps not surprising, since atropine, an "alkamine ester" (Dawes, 1946a, 1946b), has much in common with the members of this group, such as the antihistamines and the local anaesthetics. In the doses used, little subjective effect on the accommodation, gut, or heart rate was observed by the volunteers.

Objective Phenomena.—The subjects did not look flushed, and their pupil size was variable—several of them having dilated pupils, others being unaffected. Some of them looked obviously drowsy and heavy. All were able to read and write, accommodation being hardly affected.

Pulse

The average pre-injection pulse rate for each subject was taken as 100% and the post-injection rates were expressed in percentage form. The mean values of these percentages for all subjects combined at various intervals of time after the administration of the drugs were then calculated, and are presented diagrammatically in Fig. 1.

FIG. 1.—Mean pulse rate after injection of atropine sulphate and atropine mucate.

The pulse showed great variation throughout the experiments. With both the sulphate and the mucate there was an initial slowing, followed by a rise above the pre-injection level. The magnitude of this rise appeared to be similar with both salts. The pulse rate then gradually slowed, and was still declining in rate when the experiments ended many hours after the injection.

The final rates were well below the pre-injection level. We have no knowledge of whether the pulse would have returned to the "normal" level had the observations been continued long enough. We feel, however, that the "normal" pulse rates may in fact have been elevated owing to the natural excitement before such an investigation.

Saliva

Although there was but little difference between the average pre-injection saliva values of each subject on the two days occupied by the experiment (see Table I) these "normal" salivary indices varied considerably between the subjects.

TABLE I.—Difference Between the Means of the Pre-injection Saliva Values

Subject	Before Mucate	Before Sulphate	Difference (S-M)
L. M.	6.40	6.13	-0.27
J. C.	7.65	7.22	-0.43
D. D.	3.97	4.27	+0.30
A. H.	8.17	8.42	+0.25
R. L.	5.27	5.02	-0.25
D. C.	8.30	7.30	-1.00
S. G.	6.42	5.07	-1.35
K. H.	5.00	5.61	+0.61
W. W. M. . . .	5.54	4.73	-0.81
			-2.95

Mean of the differences = -0.329 ± 0.216 ; $t=1.53$; $t_{.05}=2.31$, therefore not significant.

Because of this the results were treated in a similar way to those of the pulse rates—the average pre-injection values being taken as 100% and the post-injection saliva values expressed in percentage form. The means of these percentages based on all subjects are presented diagrammatically in Fig. 2 for various intervals of time. From this diagram

FIG. 2.—Mean saliva values after injection of atropine sulphate and atropine mucate.

it appears that, on the average, mucate of atropine reduces the salivary index 56%, and sulphate of atropine only 46%, of the pre-injection level: also that these minimum levels are reached with both drugs at one hour after injection. Consider, however (Table II), the individual minimum levels and the times at which they were reached.

The statistical test indicates that from these data we are unable to demonstrate any real difference between the mini-

TABLE II.—Minimum Salivary Indices, and the Intervals after Injection at Which They were Attained

Subject	Mucate		Sulphate		Difference in Minimum Levels (S-M)
	Minimum Level % of Normal	Time	Minimum Level % of Normal	Time	
L. M.	34.4	hrs. 1 30	48.9	hrs. 1 00	+14.5
J. C.	34.0	1 00	54.0	0 40	+20.0
D. D.	37.7	1 00	37.4	1 00	- 0.3
A. H.	59.9	1 30	62.9	1 20	+3.0
R. L.	30.4	0 40	11.9	0 40	-18.5
D. C.	45.8	1 20	47.9	0 20	+2.1
S. G.	28.0	0 40	35.5	1 40	+7.5
K. H.	52.0	1 00	60.5	1 00	+8.5
W. W. M. . . .	52.3	0 40	61.3	1 00	+9.0

Mean difference = 5.1 ± 3.62 ; $t=1.41$; $t_{.05}=2.31$. Not significant.

imum levels of the salivary index attained by the two drugs. It can also be seen that the earliest time a minimum level was recorded with mucate was 40 minutes, and the latest time 1 hour 30 minutes. With sulphate the corresponding times were 20 minutes and 1 hour 40 minutes.

The minimum levels as recorded are not, however, strictly accurate. From the records of one subject, for example, we know that at 40 minutes his saliva level had been reduced to 44%, at 1 hour to 34%, and that at 1 hour 20 minutes it was back again at 52%. Whether it went below 34%, either between 40 minutes and 1 hour or between 1 hour and 1 hour 20 minutes, cannot be established. These considerations have still more force in other subjects—and in any further experiments the necessity of taking recordings more frequently during the period 40 minutes to 1 hour 30 minutes to establish the precise minimum is evident.

Return to Normal

Although there is not enough evidence to justify a conclusion that a lower level of secretion is reached with mucate of atropine the trend of the two curves (Fig. 2) suggests that with mucate a longer time is taken to return to the normal range than with sulphate. This is the next issue to examine.

As a first approach, the mean difference between the paired readings with mucate and sulphate was calculated at all points of time where nine paired readings were available—in the same manner as was done in Table II for paired minimum readings. The results are shown in Table III.

TABLE III.—Mean Difference Between Paired Salivary Indices at Specified Intervals after Injection (Following Attainment of Lowest Level)

Time after Injection	Mean Difference (S-M) $\pm$ S.E. (9 Subjects) % of Normal	t
1 hour	+9.6 $\pm$ 4.70	2.05
1 hour 20 min. ..	+3.9 $\pm$ 4.65	0.84
2 hours 20 min. ..	+17.3 $\pm$ 5.24	3.30*
3 hours	+20.4 $\pm$ 5.70	3.58†

* Significant at 5% level. † Significant at 1% level.

At every point of time, as is also evident from Fig. 2, the level of the mean salivary index was lower with mucate than with sulphate. At 1 hour after injection the difference amounted to 10% of normal, but was not significant. At 1 hour 20 minutes the difference was only 4%, but this alteration was not outside the range of random fluctuation. By 2 hours 20 minutes after injection the difference had reached 17%—significant at the 5% level—and at 3 hours it amounted to 20% of the pre-injection average—significant at the 1% level.

The increasing divergence of the two series indicated that the rate of return from lowest level to normal was slower after injection with mucate than with sulphate of atropine, and suggested that the fitting of suitable regression lines to each series of values, following the attainment of minimum level, would enable one to estimate the difference in time between the two drugs in returning to, say, 60%, 75%, etc., of normal. (It was not thought advisable to fit curves to the complete series—from injection to reattainment of normal range—because of the doubt about the precise value of the minimum points.)

Test of Deviation from Linear Regression

Statistical tests showed that during return to normal the relationship between the values of the salivary index and intervals of time after injection did not depart significantly from linearity. In other words, no significantly better fit would be obtained by using a curved rather than a straight regression line.

The essential data of the tests are given in Table IV. In the mucate series those values of the salivary index between 1 hour and 5 hours 20 minutes inclusive, and which were

TABLE IV.—Analysis of Variance of Salivary Index at Different Times after Injection with Atropine Mucate During Return to Normal

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square
Within time groups (error) ..	93	15,462.97	166
Between times	15	36,129.94	2,409
Total	108	51,592.91	

$F = 2,409/166 = 14.5$; $F_{.05} = 1.78$

Analysis of Sum of Squares for the Time Means

Between times (above)	15	36,129.94	
Linear regression	1	33,840.82	
Deviations from linear regression	14	2,289.12	163.51
Error (from above)	93		166

$F = 163.51/166 < 1.0$; $F_{.05} = 1.8$

based on four or more subjects, were included. In the sulphate series *all* values of the index at 20-minute intervals between 1 hour and 3 hours 40 minutes were used.

The upper section of the Table merely confirms that the mean values differed significantly at the various intervals, but it supplies the data necessary for the second half of the Table, from which we learn that the mean square corresponding to deviations from linear regression, far from being significantly greater than that for error, is, in fact, less. This indicates that nothing more than random sampling departure from linearity is present. The same conclusion is reached from Table V regarding the atropine sulphate series.

TABLE V.—Analysis of Variance of Salivary Index at Different Times after Injection with Atropine Sulphate During Return to Normal

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square
Within time groups (error) ..	58	14,374	248
Between times	8	18,041	2,255
Total	66	32,415	

$F = 2,255/248 = 9.10$; $F_{.05} = 2.11$

Analysis of Sum of Squares for the Time Means

Between times (above)	8	18,041	
Linear regression	1	17,280	
Deviation from linear regression	7	761	109
Error (from above)	58		248

$F = 109/248 < 1.0$; $F_{.05} = 2.17$

Regression of Salivary Index (y) on Hours after Injection (x)

The equations to the regression lines (shown in Fig. 2) were found to be:

$$\text{Mucate: } y = 13.95x + 35.0 \quad \dots \quad \text{A}$$

$$\text{Sulphate: } y = 22.01x + 31.38 \quad \dots \quad \text{B}$$

where x is the number of hours after injection and y is the salivary index expressed as a percentage of the average pre-injection readings. These gave the values of salivary index at hourly intervals after injection, which are presented in Table VI.

From this we see that at one hour after injection—which has already been provisionally accepted as the time at which

TABLE VI.—Values of Salivary Index at Hourly Intervals after Injection—as Calculated from the Regression Equations

Hour after Injection (x)	Salivary Index (y)	
	Mucate % of Normal	Sulphate % of Normal
1	49.0	53.4
2	62.9	75.4
3	76.9	97.4
4	90.8	—
5	104.8	—

the minimum was generally reached—the salivary index was 49% of normal with mucate and 53% of normal with sulphate of atropine. Two hours later, with sulphate it had returned to within normality (97%), but with mucate was still but 75% of normal, and in fact did not return to normal range for nearly two hours more. The equations tell us, in fact, that during the return to normal the salivary index increases on the average 14% of normal per hour with mucate and 22% of normal per hour with sulphate.

But for estimating the difference in time between returning to 60%, 70%, 80%, etc., of normality which occurred with the two drugs, the regression of x on y is a more useful instrument, thus:

$$\begin{aligned} \text{Mucate : } x &= 0.06713y - 2.15955 & \dots & \text{C} \\ \text{Sulphate : } x &= 0.04351y - 1.27754 & \dots & \text{D} \end{aligned}$$

The number of hours after injection by which the salivary index had returned to 60, 70, and 80% of normal, as estimated from equations C and D, is shown in Table VII.

TABLE VII.—Difference in Time of Returning to Specified Percentages of Normality with Mucate and Sulphate of Atropine

Percentage of Normal	Hours after Injection		Difference (Hours)
	With Mucate	With Sulphate	
60	1.87	1.33	0.54
65	2.20	1.55	0.65
70	2.54	1.77	0.77
75	2.88	1.99	0.89
80	3.21	2.20	1.01
85	3.55	2.42	1.13
90	3.88	2.63	1.25
95	4.22	2.86	1.36
100	4.55	3.07	1.48

Thus, for example, if more than 25% depression of normality is regarded as essential for satisfactory drying of secretions before an anaesthetic, two hours represents the time latitude during which the anaesthetic should be administered with sulphate of atropine; but with mucate an interval of almost three hours (2.88) may be permissible.

Conclusions

From the results it is clear that the peak of atropine effect, whatever the salt used, is reached about one hour after hypodermic injection. The effect then begins to wear off quickly, for the maximum action is not maintained more than half an hour beyond this. The intensity of the drying-up effect is somewhat greater in the case of the mucate, although even here only 54% depression of salivary activity occurs. It is clear, therefore, that 1/100 gr. (0.65 mg.) of either salt is in no way an excessive dose—the result being far from complete atropinization—let alone overdose. Since this dose is the one commonly employed throughout the world, it must be that the degree of partial atropinization produced is adequate in preventing excessive salivation during anaesthesia.

The results also explain the rarity of gross overdosage in infants to whom 1/200 gr. (0.32 mg.) atropine is commonly given. While 1/200 gr. probably produces an effect near complete atropinization, there are few accidents, because the adult dose of 1/100 gr. (0.65 mg.) is in reality on the small side.

In considering the duration of the atropine effect, the time taken for the subject to return to normal must be differentiated from the "clinical" or effective duration. In the former case the prolongation provided by mucate is of the order of two hours. However, the *clinical* duration is of more practical interest, and represents the duration of the anti-sialogogue action effective for the purpose of anaesthesia. The difficulty in assessing this, however, is in deciding what degree of depression of salivation would be effective. Suppose that a salivary depression less than 25% of normal is inadequate. The difference in duration of effect

between the two drugs as shown in Table VII is nearly one hour. This coincides with our own clinical opinion, but is not in accord with the eight-hour effect described by Asquith and Thomas. They, however, used 1/75 gr. (0.87 mg.), and may have regarded higher levels of salivary activity as effective.

Clinical Implications

Saliva.—The clinical question which arises as a result of these experiments is whether atropine mucate offers any advantage over atropine sulphate in preparation for an anaesthetic. The answer depends on what is regarded as an effective level of salivary depression. This must vary with different anaesthetics, since they probably exert different stimulant effects on the salivary glands. In the case of nitrous oxide, for example, with which salivary stimulation is not great, 10% depression might be adequate. In this case the effective duration of mucate is 3.88 hours, compared with 2.63 hours with sulphate. In the case of trichlorethylene, where perhaps 25% depression might be adequate, the effective duration with mucate is now 2.88 hours, compared with 2 hours with sulphate. In the case of open ether, perhaps nothing less than 40% salivary depression might be effective. The difference in duration between the two salts is now only 30 minutes, since the mucate duration is 1.87 hours and the sulphate 1.33 hours. Whether these differences make the use of mucate worth while clearly depends on the opinion of the anaesthetist. It seems to us that the use of atropine mucate gives, in any case, rather more latitude in timing—a latitude depending probably on the anaesthetic to be used. The factor of difference in cost between the two salts seems to be very small, and can be discounted in hospital practice.

Pulse.—A brief bradycardia following an injection of atropine, before the pulse begins to rise, is well known clinically. Thus Shearer (1951), in a large series, found transient bradycardia fairly constantly, though with doses greater than 1/100 gr. (0.65 mg.). That the occurrence of bradycardia is dependent on dose is also suggested by Waters (1938), who failed to observe this effect in three subjects after 1/100 gr. Some importance has been attached to the transient bradycardia of atropine. The drug is commonly administered to prevent the muscarinic effects of neostigmine when reversing the paralysis of curare-like drugs. Deaths have been reported in these circumstances when atropine and neostigmine have been given simultaneously, and have been attributed to the slowing effect of both drugs on the heart simultaneously. The intravenous administration seems to avoid the bradycardia (Hunter, 1953), but our own findings suggest that it is still a wise precaution to give the atropine at least 5 to 10 minutes before the neostigmine.

Summary

A method is described for measuring the amount of saliva secreted following a known stimulus. This has been used on volunteers to study the depression of salivary activity produced by atropine sulphate and atropine mucate (hyperduric atropine), and to determine the relative durations of action of these drugs. The results obtained are analysed and the clinical implications discussed. Observations made on the pulse rate during the experiments are also discussed in some detail.

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