able lowering of the acidity of the gastric contents as compared with the acidity during the sucking of the dummy tablets.

A study of the acidity of the gastric contents during the first-hour control periods does not reveal any systematic difference between the hour preceding the dummy tablets and the hour preceding the alkaline tablets. In those patients who took more than three alkaline tablets in the two-hour period the acidity of the gastric contents at some time fell as low as 1 clinical unit, or 1 mEq per litre. It is an important point that under the conditions of the experiments the patients decided for themselves how many tablets to suck, subject to a tablet being in the mouth during the whole period; yet at no time was a pH higher than 6 recorded in the recovered gastric contents, most of the pH readings of more than 3 being in the range of 3 to 4. Since the alkaline tablet dissolved in water will give a pH of 10, which is probably higher than optimal, this finding that the gastric contents are not made more alkaline than the plasma is reassuring.

It may be seen from Graphs 2 and 8 that the acidity of the gastric contents did not fall immediately the alkaline tablet was sucked by these two patients. This would be accounted for if the volume of the gastric contents was large at this part of the digestive period, so that some time would be required for enough alkali to be swallowed to neutralize the whole.

At first sight it might appear that the increase of pH occasioned by the alkaline tablets was negligible, but this is not so. A slight change of pH at low pH levels represents a large alteration in the more familiar scale of units of clinical acidity. This has been made clear by charting the latter on the left-hand side and the corresponding pH of pure HCl on the right-hand side of the graphs. Thus pH 1.7 corresponds to 20 clinical units, pH 2 to 10 clinical units. In short, a change of 0.3 pH unit always represents a doubling or halving of the concentration of acid.

Discussion

It is generally accepted that reduction of the acidity of gastric contents is desirable in the treatment of patients with peptic ulcer. The experiments quoted above show that this can be achieved by sucking tablets containing quite small quantities of alkali. The question arises, What is the optimum degree of neutralization? To attain the pH of the plasma—namely 7.4—might not be advantageous, because bacterial growth might thus be encouraged. We suggest arbitrarily that an acidity corresponding to 1 clinical unit represents satisfactory neutralization.

In vitro it is found that one of the alkaline tablets neutralizes about 90 ml. of N/10 HCl, using pH 3, corresponding to 1 clinical unit, as the end-point. *In vivo* the food which the patient takes is also effective in reducing the acidity of the gastric contents, so that it is not surprising that sucking only one tablet an hour was effective in some of our experiments. Since it is quite possible to suck four such tablets an hour for a short period, it is clear that the alkaline tablets offer a potent means of reducing the acidity of the gastric contents. The question arises, Are they too potent to be given to patients without close supervision? We are satisfied that this is not the case. Douthwaite *et al.* (1952) considered the possibility of alkalosis arising from these tablets and on theoretical grounds dismissed it, provided that the daily dose did not exceed 15 tablets. Since that time many thousands of them have been used in hospital and private practice, and no such side-effect has been reported.

That the sucking of alkaline tablets will relieve symptoms of duodenal ulcer is certain. Their regular use in the symptom-free patient already seems to reduce the tendency to relapse. It would be unwise to put the case any more strongly than this for the present. It is hoped that significant results will be available after a five-year follow-up period.

Summary

The antacid effect of alkaline tablets on 12 patients with chronic peptic ulcer has been studied and compared with that of dummy tablets containing no antacid. The patients were ambulant and on full meals.

In every case the degree of neutralization was considerable, in marked contrast to the lack of effect of the control tablets.

The degree of neutralization required for therapeutics is considered and grounds are given to justify the belief that the treatment is safe.

We express our thanks to Dr. J. N. Hunt, physiology department, Guy's Hospital, for collecting and analysing the majority of the gastric samples.

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INFLUENCE OF CORTISONE ON INDUCED ASTHMA AND BRONCHIAL HYPOSENSITIZATION

BY

H. HERXHEIMER, L.R.C.P.&S.Ed.

(From the Surgical Unit and Chest Department, University College Hospital, London)

Cortisone and A.C.T.H. have been found by many authors to be beneficial in bronchial asthma. Signs and symptoms of the disorder are suppressed in the great majority of cases as long as either is administered (McCombs, 1952; Schwartz *et al.*, 1952; Lowell *et al.*, 1953; and others).

It seemed of interest to find out whether cortisone would alter the bronchial reaction to a test dose of the allergen, or, in other words, whether it would influence an induced asthmatic attack. If it did, it might also influence the course of therapeutic hyposensitization, which at present consists of a series of injections or inhalations of the allergen, the dose being cautiously increased each time. This increase aims at the gradual build-up of sufficient circulating antibody, and avoids severe reactions. If the increase is too abrupt, not only do severe allergic attacks develop but they are followed by a period of hypersensitivity (Herxheimer, 1951; Herxheimer and Prior, 1952). The mechanism of the development of hyposensitivity and hypersensitivity is, so far, not understood.

From clinical experience it was expected that cortisone would abolish or modify the violence of the reaction to an overdose of allergen, but it seemed also of great practical and theoretical interest whether it would, in addition, prevent hypersensitization.

Method

The inhalation method was used for inducing asthma and hyposensitization in the same way as described before (Herxheimer, 1951). The subject breathes atmospheric air from a closed-circuit spirometer which records his vital capacity and, in the more recent work, expiratory speed. A pump compresses air taken from the circuit and sends it at a standard pressure through an aerolyser filled with allergen extract. The aerosol thus produced flows back into the circuit and is inhaled by the patient. The degree of exposure to the allergen is measured by its duration in seconds. In order to achieve hyposensitization the duration must be

such that the exposure causes a mild attack of asthma, recorded as a slowly progressing reduction of vital capacity. The intensity of an attack is judged from the degree of reduction of the vital capacity and the time required for it. A strong attack would cause a reduction of the vital capacity already two minutes after exposure, and the reduction may reach more than 1,000 c.cm. after four minutes. In the present experiments a reduction of the vital capacity by 200–700 c.cm. was aimed at, beginning three to five minutes after exposure and reaching the maximum at about 10 minutes. The hyposensitizing effect of such a mild attack allows an increase of the duration of the exposure at the next time (after three to seven days) by 10–30%. An increase of 50% would invariably cause a much heavier attack and hypersensitization instead of hyposensitization. An increase of 100% would cause a still more violent reaction, probably an asthmatic attack lasting several days or even weeks.

The 11 subjects (see Table) were asthmatics with a long history. In seven of them the asthma was mild or moderate—that is, it did not interrupt their work and could easily be kept in check by antihistamines or sympathomimetics. In four others periods of unfitness for work had occurred repeatedly but had never lasted longer than several weeks: they had needed symptomatic treatment for the best part of the year. Five of the 11 patients were “immediate reactors”: their asthmatic reaction, if any, would occur immediately—that is, 2–10 minutes after exposure. The six others were “late reactors”: their asthmatic reaction never occurred immediately, but after a period varying from 7 to 16 hours (Herxheimer, 1952). Most of the patients had a monovalent allergy to grass pollen or house dust. Clinically

they had typical attacks only from exposure to one particular allergen, although they very often showed positive skin reactions to other allergens and might also have had mild nasal symptoms from exposure to some of these. Three of the late reactors and one of the immediate reactors suffered from asthma attacks caused by more than one allergen, and were therefore classed as suffering from polyvalent allergy. In four of the five immediate reactors and in one late reactor two or three different cortisone experiments were carried out. My conclusions are thus based on 18 different experiments.

A single experiment was designed as follows. A patient known to be sensitive to a certain allergen was exposed to his allergen extract aerosol for a period likely to produce a very mild attack. If the exposure had no such result the duration of the next exposure was suitably increased. When the desired effect had been achieved the subject received oral cortisone: during the first three days 200 mg. daily, then 150 mg. for two days, 112.5 mg. for two days, 75 mg. for two or three days, and finally 50 mg. and 25 mg. for the last three or four days. The whole course thus lasted about two weeks. The dosage during the first four days was the same in all experiments, but the decrease in dosage was speeded up in the later experiments so that the course lasted only 11 or 12 days.

The first exposure under cortisone protection was carried out on the fourth day, after the patient had had 600 mg. during the three preceding days and another 50 or 100 mg. at the beginning of the fourth. The inhalation period for the first few experiments under cortisone was at first a 30–33% increase over the previous one which had caused a mild attack and would, without cortisone, have led almost

Results

Case No.	Age and Sex	Duration of Asthma (Years)	No. of Experiment	Whether Free Intervals Longer than 4 Weeks	Clinically Sensitive to	Reaction to Inhalation	Allergic Extract Used for Inducing Attack	Period of Exposure (sec.) Used to Induce Attack		Reduction of Vital Capacity (c.cm.) by Attack			Remarks
								Before Cort.	Under Cort.	Before Cort.	During Cort.	After Cort.	
1	15 M	10 years	1	Yes	Grass pollen	Immediate	Mixed pollen	9	16	530	460	—	(1)
			2					16	32	160	785	410	(2)
2	24 F	6 "	1	"	" "	"	" "	12	20	560	700	—	(3)
			2					6	15	415	460	340	(4)
			3					20	50	830	390	75	(5)
3	30 M	6 "	1	"	" "	"	" "	14	25	645	530	265	
			2					10	20	615	330	370	
4	39 M	14 "	1	"	" "	"	" "	8	20	800	315	40	(6)
			2					16	40	250	0	0	
			3					50	150	510	700	640	
5	20 M	5 "	1	No	Grass pollen, house dust	"	House dust	105	265	425	550	1,150	(7)
6	18 M	12 "	1	Yes	Grass pollen, animal hair, moulds	Late	Mixed pollen	35	105	Attack 7 hr. later	No immediate or late attacks		
7	27 M	5 "	1	"	House dust, autumn pollen	"	House dust	4	8	Attack 17 hr. later	"	"	
			2					19	60	Attack 16 hr. later	No attack	Attack 20 hr. later	
8	26 M	6 "	1	"	House dust	"	" "	66	132	Attack 17 hr. later	No immediate or late attack		
9	41 M	10 "	1	No	Grass pollen, house dust	"	" "	36	108	Attack 8 hr. later	"	"	
10	31 F	1 year	1	"	House dust	"	" "	75	90	Attack 16 hr. later	No attack	Attack 18 hr. later	(8)
11	56 F	20 years	1	"	" "	"	" "	60	120	Attack 14 hr. later	No attack	" "	(9)

The reduction of the vital capacity in the late reactors could not be measured, because their late attacks usually occurred during the evening or later.

(1) Experiment broken off because of acute cold.

(2) Attack induced before cortisone extremely mild.

(3) Experiment broken off because of acute influenza.

(4) One week later 17-second exposure without inducing attack.

(5) Vital capacity in exposure after omission of cortisone not significantly decreased, but expiratory speed slowed down.

(6) Two weeks later 26-second exposure without inducing attack.

(7) Developed febrile tonsillitis on the day of the last exposure; this may explain the pronounced reaction.

(8) The attack after 75-second exposure was severe and lasted five days. It must be assumed that it hypersensitized the patient, who subsequently proved sensitive to much shorter periods of exposure. It has therefore been assumed that the period of exposure causing a mild attack lay between 30 and 45 seconds, although this has not been proved by experiment. The inhalation period of 90 seconds given under cortisone protection presents therefore a double or treble increase.

(9) The attack before cortisone was severe and lasted two days. Nevertheless no attack occurred under cortisone protection. The time of the late attack after omission of cortisone could not be ascertained.

certainly to a mild or moderate attack. It was found, however, that under cortisone these attacks were either extremely mild or completely absent. This encouraged us to increase the inhalation period under large doses of cortisone to double and later to treble the period which had previously caused a mild attack. Without cortisone protection such an abrupt increase must invariably be expected to cause a most violent reaction. A second exposure of the same duration was carried out when the patient had decreased his daily cortisone intake to 75 or 50 mg., a third a few days after the end of the cortisone course, and a fourth about two weeks later.

In the later experiments the second or third exposure was omitted and only three exposures were made, one under large, one under small cortisone doses, and one after the cortisone influence had ceased. Skin tests were carried out before, during, and after the course, and the blood pressure, weight, and subjective impressions of the patients recorded. No changes of blood pressure or weight were found. There was no oedema of the ankles. In one case there was slight "mooning," and in several cases the patients reported increased appetite, or nycturia, or a mild degree of sleeplessness, particularly towards the morning.

Recently two patients* were found in whom, contrary to previous experience, cortisone neither suppressed nor modified the response to a 30-33% increase of antigen dosage. It was thought inadvisable to double or treble the antigen dosage in these patients, and they are not included in the results.

Results

The results of the 18 experiments are included in the Table. Two of the experiments could not be completed because of intercurrent febrile infections. In the attacks before cortisone medication the reduction of the vital capacity was between 160 and 830 c.cm., and it occurred within 5 to 10 minutes. Under high cortisone dosage, when the period of exposure was doubled or trebled, the reduction was between 0 and 785 c.cm., and it occurred within 4 to 15 minutes. After omission of the cortisone the reduction was between 0 and 640 c.cm., and it occurred within 7 and 15 minutes. It is noteworthy that in eight experiments carried out during or after cortisone it took longer than 10 minutes to reach a significant reduction of the vital capacity. These figures show that in the immediate reactors the exposure to very large amounts of allergen was followed under cortisone by the same mild reaction which had been demonstrated after much smaller amounts of allergen without cortisone. In some cases the attacks under cortisone were even milder than those seen before, and this persisted when cortisone was omitted. In our experience this was evidence that tolerance to double or treble the amount of inhaled allergen (hyposensitivity) had been established. If this was correct we should have been able, in consequence, to increase the inhalation period further in the way which had become the routine without cortisone protection. We were able to do this in all cases.

The seven experiments with the "late reactors" differed from the others in so far that no reactions occurred under full cortisone, under reduced cortisone, and immediately after its omission. After the effect of cortisone had disappeared, mild attacks occurred in three experiments. When the exposure was repeated these attacks disappeared. It is interesting to note that this phenomenon occurred in one experiment with the subject (Case 7) who underwent two similar experiments. In the first the inhalation period was doubled and no reaction occurred after the cortisone effect had disappeared. In the second it was trebled, and a mild attack occurred after cortisone protection had ceased.

*In one of these patients the reason for this failure has now been discovered. The lowest amount of allergen capable of inducing a mild attack had not been determined accurately enough, and the experiment had been started with too large an amount of allergen as a basic value. It has now been repeated, with a satisfactory result.

Among the immediate reactors there was one exception (Case 3) from the general experience. In this experiment the attack under reduced cortisone dosage was more severe than under high dosage. It was feared that without cortisone the reaction might become too severe, and the inhalation period was therefore accordingly reduced the next time. When the whole experiment was repeated with the same subject two months later no severe reaction occurred after any of the exposures.

The skin tests did not show any decisive changes under cortisone influence. The immediate weal and flare were not suppressed in any of the cases. In two of the immediate reactors we had the impression that the skin reaction was not as intensive under cortisone as it was before. In these two cases there had been a considerable area of redness and oedema secondary to the local weal and flare. In four of the patients late positive skin reactions occurred, consisting of a local area of redness and slight swelling. These reactions were not influenced by cortisone, although suppression of the late tuberculin reaction by cortisone has been reported frequently.

The size of the weal and flare areas showed some variation on repeated testing, and sometimes an allergen showed a positive result, whereas it had been negative before or was negative afterwards. These variations were quite irregular and could not be attributed to the cortisone influence.

Discussion

An obvious possible objection to these experiments is the absence of controls. I am unable to fill this gap except from previous experience. We know what happens if a patient is exposed to an overdose of his allergen. In every case a violent attack with more or less serious consequences (hypersensitization) has followed, whether the overexposure occurred from ignorance (as in the first experiments) or by a technical error. Moreover, we have seen that attempts to increase the dosage by more than 33 to 40% above the previous exposure regularly produced too violent a reaction; since then every precaution has been taken to avoid even such minor overexposures; to double the exposure time without cortisone protection merely in order to provide a control experiment can hardly be justified.

It must be regarded as certain that without cortisone protection violent attacks would have occurred in both immediate and late reactors. It would have been expected that cortisone, so efficient in severe chronic asthma, would suppress every sign of an induced severe attack. The attacks were, however, not completely suppressed. In some of the late reactors a mild attack reappeared after the cortisone action had ceased, and in the immediate reactors the violent attack was modified into a harmless and transient wheeze. Cortisone therefore does not abolish the immediate acute attack, and it must be remembered that it does not abolish the immediate skin reaction either. There is a definite difference between the cortisone effect in the immediate and late reactors, but I cannot explain this difference.

The facts suggest that under cortisone protection an overdose of antigen has not the violent effect it otherwise would have. The after-effect is also different: no hypersensitization follows. On the contrary, the same overdose may be repeated under small cortisone doses, and later without it, without any stronger reaction than before. We see, therefore, that the mild attacks caused by a sudden twofold or threefold increase in antigen dosage (overdose) under cortisone have the same effect as the mild attacks caused by an increase of 20 to 25% without cortisone protection—that is, the development of tolerance to the higher dose (hyposensitization). The difference is that under cortisone protection a higher level of tolerance is quickly reached. This might be explained by supposing that hyposensitization is effected by the formation of a larger amount of circulating antibody in the blood, and that the more antigen is supplied the more antibody is formed. Normally, a sudden large supply of antigen leads to a violent reaction and to a condition in which the body remains more sensitive than

before—that is, hypersensitive. The mechanism of this is not understood, but it seems that cortisone suppresses it and, at the same time, allows hyposensitization to proceed undisturbed and on a larger scale than would otherwise be possible.

This action of cortisone is very different from that of sympathomimetics and antihistamines. These substances are capable of protecting against or suppressing minor and even major attacks caused by overdoses of antigen; but as soon as their effect has faded the violent reaction to the overdose becomes apparent and requires a new dose of sympathomimetic; it seems that hypersensitization as a secondary effect cannot be avoided, although this can be deduced only from general experience. Evidence from experiments is still lacking.

Our experiments have so far been done on patients with mild or moderate asthma who were either in an asthma-free interval or had chronic asthma of moderate intensity kept under control by small amounts of drugs. Whether the same effect can be achieved with severe cases of asthma remains to be seen. We know from clinical experience that the continuous severe asthmatic reaction to the allergen can be suppressed by cortisone, and that it continues to be absent for a short time after the omission of the cortisone. Gradually, however, the asthma returns. One might think that in these cases the hyposensitizing effect which may develop under cortisone is soon replaced by the hyposensitizing mechanism which has been present before.

We shall not be able to understand these observations until the action of the cortisone is more fully understood. It may be concluded, however, that in certain types of asthma hyposensitization is greatly facilitated by cortisone.

One practical conclusion follows. It will be possible to shorten the cumbersome process of hyposensitization by proceeding in bolder steps under cortisone protection. So far the therapeutic success of hyposensitization has been poor, in spite of the sometimes enthusiastic statements in many textbooks of allergy (see also Rackemann, 1932; Unger and Wolf, 1943). Hurst (1943) has expressed strong doubts of the efficacy of hyposensitization, and Herxheimer and Prior (1952) have shown that objective success is rare and can probably be achieved in only 2.5 to 4% of all asthmatics. With the help of cortisone it may be possible to by-pass some of the otherwise unavoidable setbacks, and perhaps to extend the procedure to patients with polyvalent allergy in whom this treatment so far has been less successful.

Summary

In 18 experiments on 11 asthmatic patients the amount of inhaled allergen causing a mild attack was determined. The patients were given cortisone, and when under its full influence were exposed to double or treble the amount of the same allergen. This exposure was repeated when cortisone dosage had been reduced and again after the cortisone influence had ceased.

The doubling or trebling of the amount of inhaled allergen, which normally would have caused a violent and severe attack, caused under cortisone influence either a very mild and transient attack or, in the late reactors, no attack at all. The same overexposure under reduced cortisone dosage had the same result, and this did not change after the omission of cortisone. In the immediate reactors the asthma attack tended to become still milder towards the end of the experiment, until it finally disappeared when the exposure was repeated a second or a third time after omission of the cortisone. In two other patients* cortisone did not influence a mild induced attack, and these patients were therefore not exposed to double or treble the antigen dosage.

*See note at foot of page 186.

It is concluded that, in most moderate and mild cases of asthma, cortisone protects the patients from the violent attacks through overexposure. Moreover, it prevents the otherwise unavoidable hypersensitization and permits hyposensitization to develop in spite of over-dosage.

Cortisone can therefore be used to speed up the process of hyposensitization.

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FATAL BRONCHIAL ASTHMA A REVIEW OF 18 CASES

BY

C. KELMAN ROBERTSON, M.D., F.R.C.P.Ed.
D.P.H.

Assistant Physician, the Royal Infirmary, Edinburgh

AND

KENNETH SINCLAIR, M.B., M.R.C.P.Ed.

Registrar, the Royal Infirmary, Edinburgh

The serious results of repeated attacks of bronchial asthma are well recognized, the usual sequence of events being that emphysema gradually develops, giving rise so often to "pulmonary failure" (Fulton, 1953) and ultimately to death. The asthmatic attack itself, however, although regarded as an annoying interlude in a patient's life, causing domestic and social upset, rarely ends fatally.

The first full pathological review of a case of asthma was given by Leyden in 1886, but during the ensuing 35 years only 15 further case reports, giving both macroscopic and microscopical details, seem to have been published. Huber and Koessler (1922) summarized those 15 cases together with six of their own. Since then at least six outstanding articles (Lamson and Butt, 1937; Thieme and Sheldon, 1938; Craigie, 1941; Rackemann, 1944; Unger, 1945; Walton *et al.*, 1951) have appeared, dealing with conjoint clinical and necropsy findings, the most recent of which stresses the low number of recorded cases and gives the opinion that this could be due to lack of recognition of the condition at necropsy.

The distressing consequences of this disease, both immediate and remote, have been recorded by various authors. Lamson and Butt considered that approximately 40% of cases may survive not more than four years of symptoms. In a review for insurance purposes Old (1933) estimated that the ratio of actual to expected deaths in 274 asthmatic subjects was 121% $\pm$ 5%. In differentiating between extrinsic and intrinsic asthma,