LEDERLE'S PERTUSSIS ANTIGEN IN TREATMENT OF WHOOPING-COUGH

REPORT OF AN INVESTIGATION

BY

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In 1940 Joslin and Christensen, having used Lederle's detoxified pertussis antigen in the treatment of a series of cases of whooping-cough, put forward the claim that, if given in sufficient dosage and at suitable intervals, it would shorten the duration of the disease and minimize the incidence of complications.

Methods of Present Experiment

In the investigation here reported there was a total of 20 cases, with an equal number of controls. The cases given antigen treatment were alternate cases admitted during the winter of 1941-2; the remainder constituted the controls. Each patient who received antigen had three injections, given at two-day intervals, consisting of 2 c.cm. of antigen intramuscularly.

The following observations were made in respect of all cases and controls: (1) Duration of stay in hospital. (2) Duration of period in which patient whooped during paroxysms of coughing. (3) Duration of period in which patient was subject to paroxysms of coughing. (4) Blood films made at intervals of 1 to 2 weeks to determine the percentage of lymphocytes. (5) Severity of disease, and complications, if any, noted.

Assessment of Cure.—Obviously it is not easy to determine exactly when a case of pertussis has ceased being so, and in this investigation patients were discharged when a good general condition associated with no coughing, whooping, or vomiting had been established. Nor can one describe the degree of severity of a particular case more accurately than by saying that it is mild, moderate, or severe. For these reasons the preceding observations were made in each case.

Results

The duration of stay in hospital is an approximate indication of the duration of the disease, as in few cases can the actual time of onset be ascertained. Consequently, as most cases were in the paroxysmal stage on admission, it was then that the therapeutic value of the antigen was investigated. The determining of the duration of the period in which the patient whooped during paroxysms of coughing was an attempt to assess the severity of the case, and it is probably true to state that, in general, the sooner whooping ceases the less severe is the attack of pertussis. The duration of the period when the patient had paroxysms of coughing only, constituted a further waning stage of the disease.

In comparing the average length of stay of antigen cases with controls we must consider them in these different respects. It will be seen from Table I that, except for the average duration of stay in hospital, the times of the antigen and control cases correspond quite closely, with the benefit slightly in favour of the latter. This indicates that the antigen did not decrease the time in hospital, nor did it lessen the severity of the disease.

TABLE I.—Average Duration

	Cases	
	Antigen	Controls
Stay in hospital	63 days	56 days
Experiencing paroxysms of coughing	58 "	54 "
Whooping during paroxysms of coughing	38 "	37 "

Age Incidence.—Pertussis is confined mainly to children under 5 years of age, and is most serious for those under 1 year. An analysis of the ages of cases in the present investigation provides the figures for Table II.

TABLE II

Age in Years	Number of Cases	
	Antigen	Controls
0-1	0	3
1-2	2	4
2-3	6	7
3-4	4	2
4-5	5	3
5+	3	1

Average age: Antigen cases, $3\frac{1}{2}$ years; control cases, $2\frac{1}{2}$ years.

The numbers in the different age groups correspond fairly well for antigen and control cases, and it is to be noted that the control cases were on the average one year younger. So the age factor does not compensate for the longer duration or the greater severity of the antigen cases.

Severity of Cases.—Cases may be divided roughly into three grades: mild, moderate, and severe. Any case which experiences a spasmodic cough without whooping or vomiting may be classed as mild. The moderate case would have a few whoops superimposed on the spasms of coughing, and the severe case would be liable to attacks of vomiting as well as whooping and coughing. Though patently a very approximate method of assessment, it is of value in showing the distribution and severity of cases, as in Table III. The controls have the greater number of severe cases, which again is of discredit to the antigen.

TABLE III

	Number of Cases	
	Antigen	Controls
Mild	4	2
Moderate	6	4
Severe	10	14

Incidence of Complications.—In this investigation 5 of the antigen and 4 of the control cases developed one or more of the usual complications. Table IV analyses these complications, and of the more serious ones—bronchopneumonia and convulsions—antigen and control cases each had a total of 4. The numbers are too small for it to be said that the use of antigen prevented or minimized the complications.

TABLE IV.—Type of Complication

	Number of Cases	
	Antigen	Controls
Bronchopneumonia	4	2
Convulsions	0	2
Diarrhoea	1	3

Lymphocyte Percentage in Blood Films

Differential white blood cell counts were performed at intervals of one or two weeks on all patients, to determine the manner in which the antigen affected the lymphocyte percentage; the results were examined in the following two ways.

In the first method a graph was drawn for each case by plotting lymphocyte percentage against time in days. Should the lymphocyte percentage decrease as the disease wanes, the resulting graph would be a decline. There are two main forms which the graph could otherwise adopt—namely, an incline in the opposite direction and a level trend. Table V analyses the trend of the graphs.

TABLE V.—Trend of Graph

	Number of Cases	
	Antigen	Controls
Decline	11	12
Level	1	1
Incline	1	2

The figures are almost identical in both antigen and control cases, showing that the administration of the antigen did not affect the percentage of lymphocytes in the blood. It is to be expected that the lymphocyte percentage would, in a case

treated by ordinary methods, approximate to its normal level as the disease diminishes, but Donald (1938) found that relative lymphocytosis persisted even to the ninth week of disease in 50% of cases. This observation would account for those cases which were not in agreement with the "decline" form of graph.

In the second method of examination of the lymphocyte percentage, the average lymphocytosis during the course of the disease was calculated for both antigen and control cases. The figures were 64% for the former and 68% for the latter. Here again no appreciable difference existed between the two groups.

Sauer (1933) and Daughtry-Denmark (1936), as a result of lymphocyte percentage counts taken during prophylaxis of children with pertussis vaccine, found that the figures were raised as in cases of pertussis. The antigen in the present investigation does not appear to have affected the course of the lymphocytosis either quantitatively or qualitatively, and it is reasonable to expect that the former, at least, should have occurred.

Discussion

From the foregoing results it is apparent that the antigen employed as a therapeutic agent in this investigation did not shorten the duration of the disease, render it less severe, or reduce the incidence of complications. Space does not permit a detailed comparison of results with those obtained by Joslin and Christensen, but it may be noted that the dose of antigen we gave was that advocated by them, and the average ages of patients in both experiments are comparable. As those workers did not include the criteria by which they assessed their cures a reliable comparison of the average duration of the two series is not possible. Among their list of complications they included bronchitis, which is not generally accepted as such but is considered an accompaniment of pertussis. By omitting these cases their complication rate can be revised, as follows:

Original percentage :	Revised percentage :
Antigen, 0.6% ;	Antigen, 0.4% ;
Control, 18.0% .	Control, 8.0% .

Thus the complication rate of their control cases appears less serious.

In the present investigation 17 out of 20 cases which received antigen were in the paroxysmal stage when admitted. It has been suggested by some workers that vaccines used in the treatment of pertussis must be given in the catarrhal stage to be effective. This remains to be proved for the antigen, and certainly merits attention.

The three cases in the catarrhal stage when injected were in hospital for 76, 60, and 33 days respectively, which figures do not suggest that any amelioration of the disease resulted from use of the antigen.

Summary

Twenty cases of pertussis treated with an antigen are compared with a similar number of controls.

Duration of the disease, complication rate, and lymphocyte percentage were not appreciably affected.

The results of this investigation are briefly compared with those of a similar experiment and discussed.

I wish to acknowledge the permission of the Medical Officer of Health of the London County Council to publish these results, and to thank Chas. F. Thackray Ltd., Leeds, for a generous supply of Lederle's detoxified pertussis antigen.

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Sarsaparilla has been used as a remedy for over 300 years, and since the earliest colonial settlement in America it has found favour there as a tonic drink. During the past 50 years there has been an extensive literature on the saponins of sarsaparilla, and according to F. M. Thurmon (*New Engl. J. Med.*, 1942, **227**, 128) only one definite saponin—sarsasaponin—has been isolated from any of the varieties of sarsaparilla. Thurmon has used sarsasaponin in the treatment of psoriasis, and found that it had a beneficial effect on 62% of the 75 patients he treated.

GASTRO-DUODENAL SURGERY IN THE AGED

BY

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With the ever-increasing progress made—perhaps even more along the lines of pre-operative preparation, anaesthesia, and post-operative care than in actual technique—certain major procedures can now be undertaken at an age which in the past would have been considered prohibitively high. Needless to say, with age and its increased incidence of respiratory infections, cardiovascular degeneration, prostatic obstruction, and so forth, one does not perform major operations without strong indications, but when those indications are present it may be unfair to the patient to make the number of his years the sole factor which denies him the benefits of surgery.

Chronic and frequently relapsing gastric or duodenal ulcers, both of which heal less readily in the aged, and carcinoma of the stomach, or their complications, all form occasional indications for surgery in the later years of life.

Gastro-duodenal Perforation

Acute perforation of peptic ulcer or carcinoma is an absolute indication for surgery. Of 83 such operations performed by me since 1936, 18 were on patients over the age of 60, and 6 over 75. In a series of 5,740 gastro-duodenal perforations taken from the literature by Sandell (1936) only 57 patients were over the age of 60, and the oldest was aged 77. In the same communication Sandell recorded the recovery of a patient of his own, aged 82, after suture of a juxta-pyloric perforation.

In my series of 18 patients of 60 and over, two were cases of perforated carcinoma of the stomach. One of these, aged 70, died after simple closure of the perforation; the other, aged 61, made an excellent recovery after an emergency gastrectomy—an operation which seemed advisable because the carcinoma was also causing obstruction. Of the remaining 16 patients with simple perforation three were aged 79 and two 77. One 79-year-old lady with a duodenal perforation of 4½ hours' duration recovered after closure of the perforation under local anaesthesia (this being the second oldest case of perforated ulcer on record to recover). One of the 77-year-old patients also made a good recovery. Of the whole 16 patients with simple perforation 10 died. On closer investigation it becomes apparent that failure to send the patient to the surgeon early, rather than age, was the factor which caused the high mortality. Of the 8 seen and operated on under twelve hours from the time of perforation six made a complete recovery and two died, four weeks and six weeks after operation, from bronchopneumonia and cerebral thrombosis respectively. With such delay the figures could hardly have been much better in youthful patients. It is obviously well worth while to operate on these aged patients if they are presented in reasonably early hours after perforation. No doubt the possibility of peptic perforation does not suggest itself so readily to the practitioner when he is confronted with an aged patient, often with intercurrent ailments and a long history of pain.

Another case—the oldest case of duodenal perforation, and possibly of duodenal ulcer, on record—came to my notice for the first time in the post-mortem room.

A feeble lady aged 91 was admitted to a "chronic ward" on June 8, 1936, complaining of general weakness and occasional lower abdominal pain, with loss of weight. Her abdomen was rather guarded, but presented no other abnormal physical sign. There were pressure sores on the heels and moist crepitations at the bases of both lungs. She became steadily weaker, and had occasional abdominal discomfort until June 17, 1936, when she complained of pain in her chest just before midnight. She collapsed later, and died at 8.15 a.m. the next day.

Post-mortem examination, performed by Dr. Allen B. Bratten, disclosed a general sero-fibrinous peritonitis with two pints of free fluid. On the anterior wall of the duodenum 1.5 cm. beyond the pylorus was an ulcer 1 cm. in diameter, perforated in its centre. Another larger ulcer was present on the posterior wall of the duodenum.