Chance Element ; Confidence Intervals

All the values of R calculated per group have been influenced to some extent by chance events, and consequently they will not be the same as the true index for the effect of vaccination, which we may call R 1. With a view to getting an impression of the influence of chance events, 95% confidence intervals were calculated; they are set out in Table IV. The limits have been fixed in such a way that there is a probability of 95% that R 1 will fall within the interval worked out from the observed values.*

In general, chance events have a smaller influence on results obtained from large groups than those obtained from small groups. Hence R values calculated for large groups represent a more reliable estimate of R 1, the true measure of the effect of vaccination. The confidence interval for a large group is normally narrower than one for a small group, and so permits of more strictly formulated conclusions.

Results

The results for the 35 groups have been assembled in Table IV. Part I relates to three groups in which sick absences failed to provide any evidence of an influenza epidemic. One remarkable fact is that an epidemic pattern was displayed by sick absences among men working in factories 2 and 3 but not by those of female employees in the same factories. The remaining 32 groups have been divided into three categories in accordance with the number of vaccinated persons they contain. It is clear that this number (if it represents less than 50% of employees) must be at least about 1,000 if the confidence interval is to be narrow enough to allow reasonably accurate conclusions to be drawn. It is seldom possible to draw such conclusions from data for smaller groups.

Results for the largest groups would indicate that the reduction in the E.I.R. can be assessed at 65 to 70%. The results for the smaller groups are not in conflict with this assessment. This would imply that vaccination resulted in a saving of 8,200 working days, or a good 70 days per 100 vaccinated persons—a saving that amply makes up for the expense incurred.

It has not been possible to determine with sufficient certainty the influence exercised by age on the I.R.s of vaccinated and non-vaccinated persons during the four-week observation periods.

Summary

The effect of an inactivated influenza vaccine on the "extra incidence rate" during an influenza epidemic was determined by studying sick absences in 35 groups, each made up of vaccinated and non-vaccinated persons and together comprising more than 45,000 persons, of whom more than 11,000 had been vaccinated.

The vaccination programme appears to have reduced extra sick absences by 65 to 70%.

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COMBINED STEROID THERAPY OF FULMINATING ULCERATIVE COLITIS

BY

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Fulminating ulcerative colitis is a serious emergency problem which fortunately confronts the clinician infrequently. However, when it does present, treatment must be urgent and immediate or the patient's life may be forfeit.

Of recent years there has been a change in the medical management of ulcerative colitis, and steroid therapy has been found to be useful in many cases (Truelove and Wits, 1955). Refinement and possibly improvement in treatment has been reported with the use of hydrocortisone intrarectally by slow infusion (Truelove, 1956, 1957, 1958) and prednisolone intrarectally from a plastic bag in one injection (Matts, 1960a, 1960b, 1961a).

Reports of the use of steroids in fulminating colitis are few. In the series presented by Lennard-Jones and Vivian (1960) only seven cases were treated in the fulminating episode with large doses of either A.C.T.H. or cortisone. Only two of these were found to improve as a result of this treatment. Truelove (1960b) reports more encouraging results using local hydrocortisone either alone or combined with systemic steroids. All his five cases reported in detail improved on treatment. Further, he cited a sharp fall in the in-patient mortality rate of ulcerative colitis patients during the years topical steroids had been used at the Radcliffe Infirmary. As the results of management of ulcerative colitis in general with steroids have been so good (Truelove, 1956, 1957, 1958, 1960a; Watkinson, 1958; Matts, 1960a, 1960b, 1961a) it would appear that their use in fulminating colitis is worth considering. Accordingly a group of 12 patients have been treated with combined A.C.T.H. by injection and intrarectal prednisolone.

Selection of Patients

Ulcerative colitis was diagnosed from the history and the findings on examination (including sigmoidoscopy). Criteria for declaring it to be the fulminating type are notoriously difficult to define. However, the criteria suggested by Brooke (1956) when combined with the clinician's general impression appear satisfactory. These are: Severe toxæmia, pyrexia to 103–104° F. (39.4–40° C.), lethargy verging on coma, and serious alterations in blood chemistry. At least three out of these four criteria were present in all cases in this series. In addition stool culture was undertaken to exclude dysenteries, and rectal biopsy done if sigmoidoscopic appearances were at all atypical. The histological changes found in the biopsy specimens were characteristic of acute ulcerative colitis as reported elsewhere (Matts, 1961b).

Therapy Used

Passive.—There can be no substitute for immediate correction of anaemia, hypoproteinaemia, and changes in blood chemistry. This usually necessitates transfusion with blood, plasma, and appropriate electrolytes. These measures must be undertaken as soon as the patient is admitted to hospital—even a few hours' delay can prove very serious. In all cases described in this paper these measures were taken within four hours of the patient's admission. As bacteraemia is a likely occurrence in ulcerative colitis, especially of the portal-vein blood (Brooke and Slaney, 1958; Brooke, 1959), all patients were put on combined therapy with penicillin and streptomycin in appropriately large dosages. Other measures always taken were the relief of pain with suitable analgesics—usually opiates—and the symptomatic treatment of nausea and vomiting with injections of chlorpromazine. Vitamins were added to the intravenous infusions, and in an endeavour to protect the liver so far as was possible from toxic damage intravenous feeding with suitable solutions was continued until the patient was able to take food well by mouth.

Active.—These passive measures for correction of deficiencies and unpleasant symptoms were combined with active steroid therapy. Prednisolone enemata (20-mg. strength) were given eight-hourly using the plastic-bag method (Matts, 1960a, 1960b, 1961a). At the same time soluble A.C.T.H. was given 12-hourly, the usual dose being 60–80 units and the route intramuscular. In some cases the first dose of A.C.T.H. was given intravenously, as the circulatory collapse at the initial stage might have caused delay in absorption with intramuscular therapy.

Results.—Nine patients recovered on medical treatment alone, two recovered after surgery, and one patient died.

Brief Case Reports

Case 1.—Boy aged 14. Two-year history of mild diarrhoea with occasional blood, three days' severe continuous diarrhoea with much blood, collapsed, vomiting. On examination: very shocked, blood-pressure 60/0, pulse 140, temperature 102° F. (38.9° C.), mentally confused, diffuse guarding over all abdomen. Sigmoidoscopy: rectum full of blood, generalized mucosal ulceration. Haemoglobin 65%; serum sodium 110 mEq/l.; serum chloride 80 mEq/l.; serum potassium 2.8 mEq/l.; serum albumin 2.8 g./100 ml.; stool culture negative. Transfused and treated with combined steroid therapy, etc. Rapid response to therapy; by 10 days was ambulant and bowel action

down to twice daily. Barium enema one month later showed moderate generalized colonic changes of ulcerative colitis.

Case 2.—Youth aged 18. Two-weeks history of increasing diarrhoea and blood loss. One day prior to admission collapsed after severe rectal haemorrhage. On examination: semicomatose, dehydrated, blood-pressure unrecordable, pulse 160, temperature 104° F. (40° C.), distended abdomen. Sigmoidoscopy: reddened mucosa, no ulceration seen. Rectal biopsy: typical acute ulcerative colitis. Haemoglobin 40%; serum sodium 115 mEq/l.; serum potassium 2.4 mEq/l.; serum chlorides 94 mEq/l.; serum albumin 3.1 g./100 ml.; stool culture negative. Transfused and treated as described. Slow initial response to therapy, but by two weeks was ambulant and bowel action twice to thrice daily. Barium enema two weeks later showed generalized mucosal changes, but the sigmoid and rectum appeared to be spared.

Case 3.—Girl aged 16. Four months' diarrhoea. Three days' severe diarrhoea with much pure blood, one day's collapse with vomiting and mental confusion. On examination: semicomatose, blood-pressure 85/20, pulse 180, temperature 103° F. (39.4° C.), flaccid abdomen. Sigmoidoscopy: typical severe ulcerative colitis. Haemoglobin 50%; serum sodium 120 mEq/l.; serum chlorides 80 mEq/l.; serum potassium 3.8 mEq/l.; serum albumin 3.4 g./100 ml.; stool culture negative. Transfused and treated as described. Rapid improvement. Ambulant in five days and bowel action twice daily. Barium enema two weeks later showed mainly left-sided changes.

Case 4.—Woman aged 68. Intermittent attacks of diarrhoea for many years, four days' very severe bloody diarrhoea, vomiting, abdominal distension, severe abdominal pain, incontinence. On examination: dehydrated, mentally confused, blood-pressure 90/30, pulse 120, temperature 99° F. (37.2° C.). Sigmoidoscopy: acute ulcerative colitis. Haemoglobin 65%; serum sodium 114 mEq/l.; serum chlorides 84 mEq/l.; serum potassium 3.4 mEq/l.; serum albumin 2.8 g./100 ml.; stool culture negative. Transfused and treated as stated. Good response to treatment, ambulant on tenth day, bowel action once daily. Barium enema three weeks later showed mainly left-sided colitis.

Case 5.—Man aged 30. Three weeks' severe diarrhoea with massive rectal haemorrhages one week before and on day of admission. Had not sought medical advice. On examination: very dehydrated, comatose, pulse about 300, temperature 105° F. (40.6° C.), abdomen very distended, bowel sounds absent, blood-pressure unrecordable. Sigmoidoscopy: reddened mucosa, no ulcers, much oozing of blood from mucosa. Rectal biopsy: acute ulcerative colitis. Haemoglobin 25%; serum sodium 106 mEq/l.; serum chlorides 60 mEq/l.; serum potassium 2.1 mEq/l.; serum albumin 1.2 g./100 ml.; stool culture negative. Massive transfusions plus other therapy. Surgery was decided upon as an immediate measure in view of delay in seeking treatment and of poor general condition. Patient, however, died 14 hours after admission, before he was fit for operation. Necropsy showed generalized ulcerative colitis with two perforations of the colon and generalized peritonitis.

Case 6.—Woman aged 67. Thirty-year history of varying diarrhoea with passage of blood. Four days' very severe diarrhoea with vomiting, collapse, abdominal pain, and distension. On examination: conscious, dehydrated, blood-pressure 70/30, pulse 180, temperature 104° F. (40° C.), abdomen tender with left-sided guarding. Sigmoidoscopy: severe ulcerative colitis. Haemoglobin 48%; serum sodium 120 mEq/l.; serum chlorides 80 mEq/l.; serum potassium 4 mEq/l.; serum albumin 2.3 g./100 ml.; stool culture negative. Transfused and treated as stated. Good response, ambulant in nine days, bowel action twice daily. Barium enema three weeks later showed generalized ulcerative colitis.

Case 7.—Woman aged 27. Six-year history of diarrhoea diagnosed as ulcerative colitis. Two days' very severe

diarrhoea with collapse and rectal haemorrhage. On examination: dehydrated, semiconscious, blood-pressure 60/30, pulse 100, temperature 103° F. (39.4° C.), abdomen distended. Sigmoidoscopy: typical acute ulcerative colitis. Haemoglobin 44%; serum sodium 114 mEq/l.; serum chlorides 78 mEq/l.; serum potassium 3.1 mEq/l.; serum albumin 2.8 g./100 ml.; stool culture negative. Transfused and treated as stated. Good response and ambulant in eight days, bowel action once daily. Barium enema four weeks later showed ulcerative colitis of transverse and descending colon.

Case 8.—Man aged 30. One-month history of mild diarrhoea, suddenly becoming very severe five days before admission. On examination: very dehydrated, blood-pressure 70/40, pulse 120, temperature 103° F. (39.4° C.), periods of mental confusion and coma, abdominal distension. Sigmoidoscopy: reddened mucosa, much oozing of blood, no ulcers. Rectal biopsy: acute ulcerative colitis. Haemoglobin 60%; serum sodium 112 mEq/l.; serum chlorides 84 mEq/l.; serum potassium 3.1 mEq/l.; serum albumin 3 g./100 ml.; stool culture negative. Transfused and treated as stated. Little response to treatment. At fifth day laparotomy was performed as conditions were unchanged. Perforation of transverse colon was found, with local peritonitis. Proctocolectomy was performed. Patient made good post-operative recovery. Specimen showed generalized ulcerative colitis with gross undermining of mucosa.

Case 9.—Man aged 62. One-year history of attacks of bloody diarrhoea. Two weeks' increasingly severe bloody diarrhoea with vomiting, abdominal pain, and incontinence. On examination: comatose, incontinent, with blood oozing continually from the rectum, abdomen distended, blood-pressure 45/0, pulse 140, temperature 103° F. (39.4° C.). Sigmoidoscopy: acute ulcerative colitis. Haemoglobin 61%; serum sodium 121 mEq/l.; serum chloride 90 mEq/l.; serum potassium 2.0 mEq/l.; serum albumin 2.8 g./100 ml.; stool culture negative. Transfused and treated as stated. Eight days later ambulant, leg-vein thrombosis but no pulmonary emboli. Bowel action once daily. Barium enema two weeks later showed dilated colon with mucosal abnormality of left side.

Case 10.—Woman aged 70. Thirty years' ulcerative colitis. Six days' history of very severe diarrhoea with much blood. On examination: abdomen distended, pulse 120, temperature 102° F. (38.9° C.), semicomatose, dehydrated, blood-pressure 80/40. Sigmoidoscopy: acute ulcerative colitis. Haemoglobin 84%; serum sodium 120 mEq/l.; serum chlorides 91 mEq/l.; serum potassium 1.9 mEq/l.; serum albumin 2.1 g./100 ml.; stool culture negative. Transfused and treated as stated. Little response to therapy. By sixth day it was decided to perform surgery. Proctocolectomy was performed and the patient made good recovery. Specimen showed generalized ulcerative colitis with multiple stricture formation.

Case 11.—Man aged 32. Fifteen-day history of increasing bloody diarrhoea. Rectal haemorrhage on day of admission. On examination: very pale, abdomen tender, mentally confused, blood-pressure 66/30, pulse 210, temperature 102.8° F. (39.3° C.), incontinent. Sigmoidoscopy: typical severe ulcerative colitis. Haemoglobin 25%; serum sodium 130 mEq/l.; serum chlorides 94 mEq/l.; serum potassium 2.9 mEq/l.; serum albumin 3.1 g./100 ml.; stool culture negative. Transfused and treated as stated. Good initial response, but relapse on fourth day with further improvement on eighth day. By three weeks was ambulant and bowel action once daily. Barium enema one month later showed ulcerative colitis of transverse and descending colon.

Case 12.—Man aged 29. Two months previously had begun to pass blood P.R. One week before admission diarrhoea 15–30 times daily and vomiting; abdominal pain. On examination: dehydrated, abdomen very tender, drowsy, temperature 103° F. (39.4° C.), pulse 180, blood-pressure 90/40. Sigmoidoscopy: severe ulcerative colitis. Haemoglobin 75%; serum sodium 130 mEq/l.; serum chlorides 84 mEq/l.; serum potassium 3.1 mEq/l.; serum albumin

3.4 g./100 ml.; stool culture negative. Transfused and treated as stated. Dramatic improvement. Ambulant in six days, bowel action once daily. Barium enema two weeks later showed ulcerative colitis of transverse and descending colon.

Discussion

The reasons for the use of intramuscular A.C.T.H. and rectal prednisolone together are threefold. Firstly, A.C.T.H. has been shown to be more effective than oral steroids in terminating the acute attacks of colitis (True-love and Witts, 1959) although the relapse rate was higher in this group of cases. This finding is supported by the impressions of Lennard-Jones and Vivian (1960) in their series. It would therefore seem logical to use the most effective agent in an emergency like fulminating colitis.

Secondly, the possibility of synergism of the various factions of the adrenal cortex exists. Synergism is often put forward to support the use of two or more therapeutic agents in medicine. It is an attractive hypothesis but notoriously difficult to prove. If synergism of certain of the adrenocortical factions did exist, then by using A.C.T.H. it would be bound to be invoked, as production of all of these will be stimulated in the adrenal cortex. The possibility that one of these factions aids the action of the intrarectal prednisolone is suggested as a reason for the good results in abating the inflammatory effects of the disease on the colon in this series.

The possibility of synergistic action between closely related substances such as steroids has been reviewed at length by Veldstra (1956). In particular there is evidence that synergism may occur when the components of a mixture are acting "in series" towards the same end-effects—for example, when antimetabolites are competing with intermediates in a biosynthetic chain. It is, of course, known (Nugent *et al.*, 1959) that different metabolic pathways are involved in the breakdown of the various steroids in the body, which may be significant in this connexion.

Further evidence that two different steroids may work better together than the same one by a combined oral and rectal route has been provided by Truelove (1960a). He obtained better results giving oral prednisolone and rectal hydrocortisone than giving oral prednisolone with rectal prednisolone. This caused him to raise at that time the possibility of synergism as an explanation for these results.

Thirdly, the concentration of steroids in the tissues when using oral steroids cannot approach that obtained by a direct local application to the recto-colonic mucosa. As many of the lesions of ulcerative colitis are mucosal or submucosal it is possible to achieve a high local steroid concentration around this zone with intrarectal therapy. Further it has been shown (Matts and Gaskell, 1961) that, using the plastic-bag method, penetration of much of the colon can be obtained. Thus the therapeutic solution will be available in high concentration where it is most needed.

It is of interest to note that the patient who died had himself delayed seeking advice for two weeks in spite of very severe symptoms. This delay may well have contributed to the failure of treatment.

There is no doubt that fulminating ulcerative colitis is a condition in which the best results can be obtained by co-operation of physicians and surgeons; the earlier therapy is begun the better the prognosis becomes. It

appears to affect the very young and the very old, and most of the patients here fall into these two categories.

The results of this small series may perhaps be taken as an indication that correctly managed medical therapy has something to contribute in the acute case of colitis. The measures taken will be bound to improve the general condition of the patient. Even if surgery is later decided upon, the risks of operation will be reduced by the adequate correction of infection and deficiencies. Adrenocortical suppression should not have occurred, but in any case operative and post-operative steroids should be given to guard against this. It is suggested that the combined steroid regime be tried in all fulminating cases, but not persisted in if there is no favourable response in a few days, or abandoned should the patient's condition seriously deteriorate on treatment. Patients with surgical complications such as perforation or haemorrhage will of course require special surgical consideration. The results with combined intramuscular A.C.T.H. and intrarectal prednisolone are possibly superior to other reported regimes of steroid therapy.

Summary

The results of treating 12 cases of fulminating ulcerative colitis are reported. Combined intramuscular A.C.T.H. and prednisolone enemata assisted recovery in nine cases, with appropriate additional measures for correction of anaemia, shock, electrolyte imbalance, sepsis, etc. A possible synergic mechanism is suggested for the effectiveness of the steroid therapy.

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A new British Standard specification (B.S. 3462: 1962) for spectacle frames made predominantly of gold-filled material or nickel silver has just been published. The standard deals with those essential requirements for metal frames which are independent of individual dimensional requirements, and incorporates a mechanical test for the frames most likely to be used by children—those made of nickel silver. The object of this test is to ensure that the bridge is of such strength that serious misalignment through rough handling is less likely to occur. Copies may be obtained from the British Standards Institution, Sales Branch, 2 Park Street, London W.1 (price 5s., postage extra to non-subscribers).

SEPSIS IN THE HOME*

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In spite of the vast number of published reports on staphylococcal infection many aspects of the epidemiology of the *Staphylococcus aureus* remain obscure. A large proportion of these publications are based on observations in hospitals, where the environment is both specialized and highly complex. The present investigation was designed to study the relationship of *Staph. aureus* to man in the far simpler environment of the home and the family.

In the remainder of this paper, when "staphylococcus" is used without qualification the species *Staph. aureus* is implied.

Material and Methods

The investigation was conducted in a small single-handed general medical practice situated in a pleasant residential area on the south side of Manchester, a large industrial city with a high rate of atmospheric pollution.

Study A

Throughout the year 1958 all septic lesions presenting in the practice were recorded. In addition, as many of the following observations were made as were practicable in each case: (1) a swab was taken from the lesion and sent for culture, (2) an anterior nasal swab was taken from the patient with the lesion, and (3) an anterior nasal swab was taken from other members of the family.

Definition of Sepsis.—An attempt was first made to describe shortly the type of sepsis it was thought desirable to study—but without success. Finally, it was decided to make a classified list of all the lesions that were to be recorded. Two criteria were applied in the selection of this list from all purulent processes: (1) the lesion should be easily accessible, and (2) it should be known to be commonly due to *Staph. aureus*. For both these reasons vaginal and urethral discharges were excluded. Throat infections were also omitted because of their complex aetiology and the great difficulty in defining them. The final list is given in Table I, and these were the lesions recorded.

TABLE I.—List of Septic Conditions Recorded in Study A

Infections of the skin
Follicular: Pustules. Furuncles. Carbuncles
Diffuse: Impetigo. Secondarily infected dermatoses
Traumatic: Secondarily infected skin wounds
Infections of subcutaneous tissues
Abscesses draining through the skin
Infections of special organs
Hands and feet: Palmar and plantar space infections. Pulp space infections of digits. Paronychia
Eyes: Conjunctivitis. Styes. Blepharitis. Dacryocystitis
Ears: Otorrhoea—acute and chronic. Otitis media. Otitis externa

Study B

This study is described in outline here as only brief reference will be made to the results. A full description of the investigation will be given in a separate communication.

Between March, 1957, and May, 1959, 37 families were investigated for periods ranging from 12 to 24

*Based on part of an M.D. thesis presented to the University of Liverpool, December, 1960, and part of the essay awarded the Sir Charles Hastings Clinical Prize, 1961.