Summary and Conclusions

The incidence of brucella infection and active disease in the Isle of Wight was assessed by a survey during the 12 months December, 1958, to December, 1959.

Four cases of clinically active disease were encountered.

Agglutination tests and skin tests indicate infection in about 17% of the adult population.

Of 685 children, 5% gave positive skin tests. Raw milk was drunk at home by 37% of children attending urban schools, and by 67% of children attending rural schools. The incidence of positive skin tests was highest (17%) among a group of 85 children who attended rural schools and drank raw milk at home.

On the basis of single examinations 33 out of 520 registered dairy herds on the island were found to be producing milk infected by *Br. abortus*.

Data were also obtained on the incidence of agglutinins and skin sensitivity among adults occupationally exposed to infection by contact with animals, as well as among others known to be drinking raw milk from infected herds.

It is concluded that infection is widespread among the dairy herds on the island. Consumption of infected milk is associated with a high rate of infection among adults and children. Much of this infection is sub-clinical, but cases of overt disease are occurring.

We are glad to acknowledge the assistance given to this inquiry by Dr. C. M. P. Bradstreet, Sir Weldon Dalrymple-Champneys, Mr. G. A. Gould, Mr. A. Sheath, Mr. A. W. Smith, Dr. H. R. E. Wallis, Dr. R. A. Zeitlin, Dr. W. S. Gordon, and many Isle of Wight medical practitioners, especially Dr. G. Gordon Brown and Mr. R. B. Grimaldi, veterinary surgeons, head teachers, and parents. Although every encouragement was given by the chairman, members, and other officers of the Isle of Wight County Council, the views expressed are our own.

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DIFFICULTIES IN WEANING IN STERIOD TREATMENT OF ASTHMA

BY

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There is general agreement that adrenocorticosteroids are useful in treating an acute attack of asthma (M.R.C., 1956b), but a good deal of discussion has arisen about their effectiveness as a long-term measure (M.R.C., 1956a). In spite of the M.R.C.'s unenthusiastic report on this long-term use, most subsequent workers have not agreed, and this opposing view is well summarized by Phear *et al.* (1960).

In practice, the usual difficulty is not to decide whether to give long-term steroid therapy to a particular patient, but how to wean a patient from treatment once symptoms are under control. It is this difficulty in weaning that is the main deterrent to giving steroids to asthmatics. Information with regard to the possibility or probability of weaning the patient suggests this is usually difficult. Thus Walton (1956), who studied 153 patients for up to five years, concluded that it "is rare that patients can stop using them [steroids] once they have started." Sheldon *et al.* (1955), who studied 51 patients for periods of up to six months, noted that relapse of symptoms was "the usual experience when the drug was withdrawn."

In the M.R.C. 1956a trial 22 of the 36 patients (61%) were still taking steroids 6 to 22 months after the trial ended; only 7 (19%) were reported to be well and off steroid treatment. Bickerman *et al.* (1954) treated 163 patients with short courses of steroids (average about 8 days, range 3 to 21 days) and noted relapse in the majority shortly after stopping treatment. Twenty-two patients were free of symptoms for more than two months, but only one had a remission lasting more than 12 months. Brockbank *et al.* (1957) treated 29 patients for up to three and a half years and reported 8 (27.6%) as being well and off steroids. Irwin and Burrage (1958) studied 68 patients for up to seven years and found that all except 3 (5%) still required steroids. Arnoldsson (1958), who also presents a very extensive review of the literature, gives details of 161 patients, of whom only two were successfully weaned. Livingstone (1958), in a general review, says "they are difficult, if not impossible to withdraw." Williams (1959) reported 202 patients, some of whom had been followed since 1951: 121 (60%) needed continuous treatment, 43 (21%) had intermittent treatment, and 38 (19%) had only a single course of treatment. Phear *et al.* (1960) treated 50 patients for three to six months, and only 6 (12%) remained well and off steroids. Of the 701 patients described, sufficient details are given about 538 to say that 463 (86%) of them were still taking steroids at the end of the period of observation. There were 21 deaths (3%).

None of the above authors set out specifically to study the problem of weaning from steroids, and it is felt that a more detailed analysis with this in mind is justified. Accordingly, a retrospective survey has been made of all patients with asthma attending the asthma clinic at University College Hospital who have had treatment with steroids. Answers have been sought to the following questions: (1) When asthma is treated with steroids is the treatment likely to be permanent? (2) Which type of patient, if any, is likely to be weaned?

President KENNEDY has announced that he is establishing a panel of medical and other experts to plan a programme of research into the causes, cures, and means of preventing mental retardation. He said in a statement that there were 5,000,000 mentally retarded people in the United States and that the number is expected to rise to 6,000,000 by 1970. (*New York Times*, October 16.)

Material and Methods

For the purposes of this study, asthma may be defined as chronic or recurrent dyspnoea associated with wheezing and without associated heart disease or obvious chest infection. It is often difficult to be sure whether some patients are suffering from asthma or chronic bronchitis or both diseases together. Patients with obviously infected sputum were excluded, but exact differentiation of these two diseases is sometimes very difficult, as is mentioned later.

Of the 135 patients who were studied from the time they started on steroids to the time of their last attendance at the clinic, 24 are no longer attending and they have not been followed up further. Also included are 20 patients who started steroid therapy elsewhere. It is possible that these latter two groups to some extent cancel each other out, but this is obviously conjecture. Fourteen of the patients started treatment after admission to hospital in status asthmaticus; the rest started treatment as out-patients or in hospital after routine rather than emergency admission.

In general, patients were given steroids when they failed to respond to routine measures and were thought to be sufficiently disabled to warrant the risks of steroid therapy. It is difficult to give more exact criteria, and undoubtedly there was subjective variation in assessing patients, both by the physician and by the patients themselves. This is an inherent difficulty in making an assessment of the severity of cases of asthma, and, while lung-function tests may offer complete objective appraisal in the future, it is doubtful if they do so at present. In any case, they were not available for the greater part of this study. Any fundamental cause was investigated and, where possible, treated.

In all patients every attempt was made to stop steroid therapy or to reduce it to the lowest possible level once symptoms had been brought under control. Routine measures such as antispasmodics, physiotherapy, desensitization, and psychotherapy were continued as seemed necessary both during and after steroid therapy. Weaning was always carried out in a gradual manner, the exact speed depending on the symptoms and response of the patient. No rigid scheme was followed, but in general the higher the dosage the more rapid the reduction. For example, a patient taking 60–80 mg. of prednisone daily would probably be reduced by 10 mg. a day to 30–40 mg. a day; then by 5 mg. every other day to 15–20 mg. a day; then by 5 mg. twice a week to 10 mg. daily; then by 2.5 mg. a week down to 2.5 mg. a day, on which he might stay for two to three weeks before stopping altogether. This scheme was very elastic and would be slowed down, speeded up, or even reversed, according to the patient's response.

The 135 patients (72 females and 63 males) were studied for an average period of 27.7 months; 63 were studied for from two to eight years, 26 for between one and two years, and 46 for less than one year.

Length and Type of Treatment

Patients were started on treatment at ages varying between 13 and 75 (average 40.1 years: females 43.6, males 37.5 years). They had suffered from asthma for an average of 17.6 years. Cortisone and A.C.T.H. were mainly used up to 1956–7, but since then the newer analogues prednisone, triamcinolone, and dexamethasone have been used almost exclusively. No attempt

is made here to differentiate between these drugs. Sixty-nine patients have been on maintenance prednisone long enough (usually not less than three months) to make assessment of the average dose possible (Table I).

TABLE I

Dose of prednisone in mg./day	2.5	5	7.5	10	12.5	15	20
Number of patients	1	12	19	26	5	4	2

TABLE II

	No.	Females	Males	% of Total
Group A—continuous treatment ..	66	31	35	48.9
„ B—intermittent treatment ..	43	26	17	31.9
„ C—no response to treatment ..	10	4	6	7.4
„ D—single course treatment ..	10	7	3	7.4
„ E—seasonal asthma ..	6	4	2	4.4

TABLE III.—Relation of Age at Onset of Asthma to Group of Asthma (See Text)

Group	Age (in Years) at Onset of Asthma													
	0–2	3–9	10–14	15–19	20	25	30	35	40	45	50	55	60	65
A	10	12	1	6	7	4	2	6	6	7	2	1	0	2
B	9	8	4	4	3	1	3	3	3	2	1	0	1	1
C	0	4	—	0	0	0	0	3	1	2	0	0	0	0
D	1	3	0	0	2	2	0	1	0	0	1	0	0	0
E	1	1	2	0	0	1	1	0	0	0	0	0	0	0
	21	28	7	10	12	8	6	13	10	11	4	1	1	3

For the purposes of further study the patients have been divided into five groups (Table II).

Table III gives the age at onset of asthma in each group and shows there was no obvious difference among the five groups. There was also no obvious difference in the incidence of family history or a past history of allergic diseases in the five groups (except in group E, who all had hay-fever).

Results

When last seen 102 (76%) patients (51 (71%) females, 51 (81%) males) were still taking steroids, and 33 (24%) patients (21 (29%) females, 11 (19%) males) were off steroids.

Only five of the 14 patients who started steroid therapy after admission to hospital in status asthmaticus required continuous therapy. This is a smaller proportion than among the patients as a whole (48.9%), but is not statistically significant ($P=0.55$).

Group A.—These patients remained on steroids continuously. Included in this group are 11 who stopped treatment for periods of less than a month; all of them relapsed on cessation of treatment, which was usually restarted at their next attendance at the clinic. It would be misleading to count these short intervals off treatment as remissions. The other patients in this group relapsed while the dose of steroids was being reduced so that treatment was continuous.

Group B.—These patients had two or more courses of treatment, with intervals between courses of more than one month, the total number being 125, distributed as follows: 22 had two courses, 8 had three, 9 had four, 3 had five, and 1 had six. There were 89 periods off treatment, of varying duration: more than 12 months, 25 periods; 6–11 months, 14; 3–5 months, 18; 1–2 months, 32. During these periods off treatment rather less than half the patients were well or improved for some part of the time. The rest seemed to start

wheezing, usually within less than a fortnight, no matter how gradually steroids were withdrawn. They were studied for an average of 32.5 months, during which time they were on steroids for 15.2 months and off for 17.3 months. When last seen 36 of the 43 were on steroids. This unusually high proportion is statistically significant ($\chi^2=19.8$, $P=0.001$), and suggests that the longer the period of observation the more chance there is that the patient will require steroids. Another significant observation was that of the 14 patients with asthma of late onset—that is, after 30 years of age—all were taking steroids when last seen ($\chi^2=14$, $P=0.001$). This suggests that the likelihood of requiring steroids permanently is greater in asthma of late onset, and is in agreement with the general impression that this type of asthma of late onset is usually more severe in type (Livingstone, 1958).

Group C.—These patients had 18 courses of treatment between them without showing any marked benefit. There were other patients, not included here, who, while not responding initially, later responded to a larger dose. It is difficult to be certain how many of these patients were suffering predominantly from chronic bronchitis.

Group D.—This is a small and rather unsatisfactory group for the purposes of analysis. Seven of these 10 patients were under observation for less than a year, and it is too early to comment further about them. Of the other three, treatment was stopped in one because a duodenal ulcer developed, and in another because of psychological disturbances. Eighteen months after stopping treatment both were still considerably disabled by asthma, but not enough to warrant the risks of restarting steroid therapy. The other patient was given A.C.T.H. for three months in 1953 with only moderate benefit. He was noted to be chronically wheezy, with occasional exacerbations, when last seen in 1957.

Group E.—These patients were troubled mainly by asthma in association with hay-fever in the summer months. This type of asthma is usually less severe and may be controlled by simpler measures, but in these six patients symptoms were incapacitating and could not be alleviated. Two have had repeated courses in the last two summers. Repeated treatment was not always necessary, as three other patients had had a single course of treatment two, three, and five years previously. The other patient has been under observation for only 10 months.

Complications and Deaths

In 13 out of the 135 patients treatment was stopped because of complications: dyspepsia in 5, psychological disturbances in 5, pregnancy in 1, reaction to A.C.T.H. in 1, renal tuberculosis in 1 (previous reported M.R.C., 1956a). Two of these have been discussed already (group D). The patient with renal tuberculosis was still chronically wheezy and disabled five and a half years after treatment was stopped. Her initial response was not spectacular, and the danger of a recurrence of tuberculosis has caused steroids to be withheld.

There were five deaths (3.7%). It is not possible to say whether there were any deaths among those patients who are no longer attending the clinic.

Case 1.—This patient, a frail woman, died in 1957 aged 78. She was on prednisone 20 mg. t.d.s. at the time of death, which occurred two days after her admission to hospital in status asthmaticus. Asthma had begun at the age of 69, and she had been to hospital 14 times. For

the last four years she had been on continuous steroids, but this treatment had not prevented the last seven admissions. Necropsy was not performed.

Case 2.—This patient, who died in 1957 aged 53, had been on steroids for four years, and was taking prednisone 5 mg. t.d.s. at the time of his death. His asthma was very satisfactorily controlled and he was well and at work the day before he died at home after an illness lasting 12 hours. He was unconscious for the last six hours. The coroner's post-mortem examination showed pneumonia of the right middle lobe, chronic bronchitis, and tenacious mucopus. The brain and adrenals were macroscopically normal.

Case 3.—A married woman aged 29 died in 1958 in status asthmaticus at home while not on steroids. A very severe asthmatic, with numerous hospital admissions, she had had steroids intermittently for four years. The last course was given seven months before she died, and since that treatment she had had a normal delivery at full term.

Case 4.—This patient, a married woman aged 56, died in 1955 in status asthmaticus at home. She was severely asthmatic, and was inadequately controlled on cortisone 25 mg. t.d.s. Further cortisone caused oedema. Dosage of steroids had not been increased.

These last two patients seemed to die owing to lack of steroids rather than because of them.

Case 5.—A woman aged 23 died in 1956 of primary amyloidosis two years after her last course of steroids. Asthma had been mild and easily controlled during this time.

This death seems to have been unrelated to steroids.

Conclusions

Of the 135 patients studied, 6 were predominantly seasonal asthmatics (group E) and 10 were possibly mainly suffering from chronic bronchitis (group C), so that the rest may be classed as cases of chronic intractable asthma. Of these 119 patients, 66 (55.5%) required continuous steroid therapy. In an approximately similar group Williams (1959) found that 60% needed continuous treatment. Of the patients on intermittent treatment nearly one-half had been on steroids for more than six months when last seen, and there was a marked tendency for treatment to become continuous, especially in patients with asthma of late onset. The only patients who seem likely to remain off for any predictable period of time are those who do not benefit. Seasonal asthma appears to be the most likely type to respond to intermittent therapy, but this may have to become permanent. However, quite long periods off treatment are possible—there were 25 longer than a year—but it has not proved possible to say which type of case will have long remissions.

The complications seem not too severe; but it must be remembered that 24 patients have been lost to the follow-up, and it is possible that some of these had complications.

In the present state of knowledge it is difficult to exonerate steroids as contributing to the death of one of the five patients (Case 2). In Case 1 the exact cause of death was not known.

Summary

A series of 135 asthmatic patients who have had treatment with steroids have been studied for up to eight years (average 27.7 months). About half stayed on steroids continuously. The rest were mainly weaned at the expense of some discomfort and showed a significant tendency to need continuous treatment, which was

especially noticeable in patients whose asthma started after the age of 30. Those most easily weaned were patients whose asthma was seasonal, usually in association with hay-fever, and those whose asthma did not respond. Apart from this, there were 25 periods off treatment lasting more than a year.

Conclusions similar to those of this study are drawn from a review of the literature.

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MECKEL'S DIVERTICULUM IN CHILDHOOD

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This paper presents a series of 82 children with Meckel's diverticulum. The series was collected in order to obtain facts and figures about the clinical picture of this abnormality in local children to strengthen clinical recognition and provide greater accuracy in teaching. Local studies can also reveal, on occasion, differences of incidence which may suggest the need for a more thorough search for local precipitating factors in the child's environment.

A second reason for studying Meckel's diverticulum in children was the need to estimate its importance as a cause of abdominal pain. One of the most frequent and perplexing problems in paediatrics, both in hospital and in the home, is to know how to manage a child with recurrent abdominal pain, and to decide how far the problem should be investigated. The detailed study of conditions giving rise to abdominal pain is therefore essential if we are to teach students how to manage the everyday illnesses they will frequently meet, and how to recognize early the less common diseases which are potentially serious if delay in diagnosis occurs.

Meckel's diverticulum takes its name from its description in 1809 by Johann Friedrich Meckel, then professor of anatomy at Halle. Diverticula of the intestine had been described before this, but he was the

first person to give a detailed account of the diverticulum and to show that it was a remnant of the vitello-intestinal duct. His evidence for this rested on the following observations: more than one diverticulum with the same structure as the small intestine is never found in the same embryo; the diverticulum is always in the distal part of the small intestine, and it always appears on the antimesenteric border. He also pointed out that the diverticulum is seen in many animal species, but only in those having a yolk sac. He posed a question which he was unable to answer and which remains unanswered to-day—namely, why the duct or some part of it persists (Meckel, 1809; quoted by Söderlund, 1959).

A Meckel's diverticulum consists of remnants of the vitello-intestinal duct, either in whole or in part. If completely patent there will be a vitello-intestinal fistula; a partially patent duct gives rise to a Meckel's diverticulum, an enterocystoma, or a cyst open at the umbilicus, depending upon whether the patent segment is at the inner, middle, or external end of the duct. The only conditions likely to be mistaken anatomically for a Meckel's diverticulum are duplications of the bowel and enterogenous cysts, but a Meckel's diverticulum has its own blood supply and is on the antimesenteric border of the bowel, whereas duplications are intramesenteric and share the same blood supply as the normal bowel.

The incidence of Meckel's diverticulum varies somewhat in different accounts. Harbin (1930) made a systematic search in 500 consecutive laparotomies in infants and children and found a diverticulum in 1.3%, whereas Rosenfeld (1955) found one in 4.5%. Söderlund (1959) looked particularly for a diverticulum in 1954 appendicectomies in Stockholm children and found one in 3.2%.

Meckel's diverticula are said to be commoner in males than in females, and Gross (1953) has a ratio of 3:1 in his series. Söderlund (1959) makes the interesting point that in his series a pathogenic diverticulum—that is, one that is definitely the cause of the patient's symptoms—was five times as common in males as in females, whereas the sex incidence was almost equal in those discovered as an incidental finding. This is borne out in the present series: 49 pathological diverticula occurred in boys and only nine in girls, while silent diverticula were present in 13 boys and 11 girls.

Present Series

The series consists of 82 children from Newcastle upon Tyne and near-by towns who have been found to have a Meckel's diverticulum. They can be classified into three groups (Table I).

TABLE I.—*Clinical Picture in 82 Children with Meckel's Diverticulum*

Group 1: Causing intestinal obstruction	..	..	..	28
By bands, volvulus, etc.	..	..	..	15
By intussusception	..	..	..	13
„ 2: Producing other symptoms	..	..	..	30
Umbilical fistula or sinus	..	..	..	8
Haemorrhage from peptic ulceration	..	..	..	17
Diverticulitis	..	..	..	4
Torsion of diverticulum	..	..	..	1
„ 3: Asymptomatic diverticula	..	..	..	24
Found at laparotomy for intussusception	..	..	..	10
Found at laparotomy for other reasons	..	..	..	14

As Brookes (1954) has pointed out, the complications of Meckel's diverticulum are more likely to occur in young children. In this series 22 children were under 1 year of age and 25 were aged 1, 2, or 3 years. These figures are broadly comparable with other series, though