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OXFORD EPIDEMIC OF BORNHOLM DISEASE, 1951

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Sylvest (1934) gave a very full description of the recorded outbreaks of Bornholm disease up to 1931. Since that time there have been many valuable reports, but most of them have dealt only with the clinical features of the disease (Pickles, 1937; Howard *et al.*, 1943; Nichamin, 1945; Scadding, 1946; Hamburger and McNeil, 1947). Practically all the large outbreaks reported have occurred in relatively closed communities, although Harder (1936) described an epidemic in the general population of Cincinnati, Ohio. So far as can be ascertained there has been no published report of any extensive outbreak occurring in the general community in this country.

This article is based on experience obtained during an epidemic of Bornholm disease in Oxford from September to November, 1951, a preliminary report of which was given (Davies and Warin, 1951) when the epidemic was still in progress. Following this preliminary report, several letters appeared in the correspondence columns, giving experience elsewhere, and from these, together with a number of private communications and information obtained through the Public Health Laboratory Service, it would appear that this country experienced a high incidence of Bornholm disease from about April until November, 1951. A total of 277 Oxford cases were eventually collected, of which 262 were visited by one of us (J. B. M. D.) or by the health visitor seconded to the investigation. From this material it has been possible to obtain useful information on the epidemiological, clinical, and virological aspects of the disease.

By following fortunate clues we were able to recognize the existence of the outbreak soon after it started, and so were able to draw the attention of the local medical profession to this largely unfamiliar disease, at the same time requesting the notification of all cases. There was a most gratifying response, and notifications were received from more than half the doctors practising in the city. One doctor notified 26 cases, the next highest being 14, and there were 25 doctors who notified 5 cases or fewer. We believe that we were informed of most of the cases which sought medical advice. However, about half our cases never went to a doctor but were found by members of the medical or health-visiting staff of the Health Department, and there is no doubt that many more mild cases remained undiscovered.

Epidemiology

It is now known that a few sporadic cases occurred in Oxford in August, but the epidemic began abruptly in the second week of September and extended over a period of six weeks, until the fourth week of October, when it ended as suddenly as it had begun, although a few cases were reported during the next three weeks. The incidence is shown in Fig. 1, and it will be seen that the peak occurred in the first week of October, with 53 cases.

The weekly incidence of cases given by Harder in the outbreak in Cincinnati (population 455,000) is

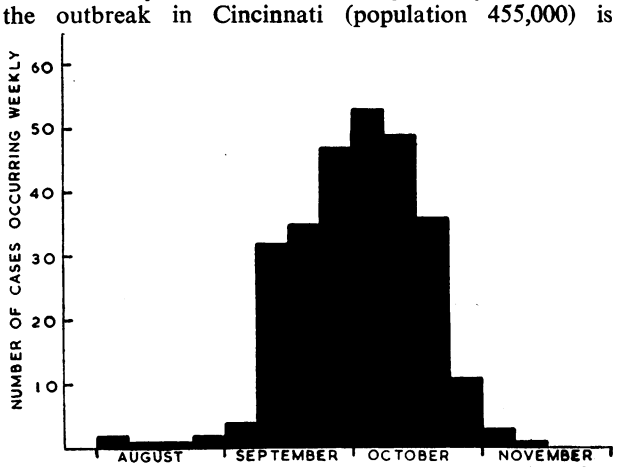

FIG. 1.—Weekly incidence of cases of Bornholm disease in Oxford during August–November, 1951.

remarkably similar to that observed in Oxford (population 106,400). It is of interest to note that the Oxford epidemic showed the same seasonal incidence as described by Sylvest and others.

Cases were spread throughout the city, but there were five distinct areas of high incidence. Two of these (North Oxford and Central Oxford) were situated on the west side of the Rivers Cherwell and Isis, which divide the city from north to south, and the other three (East Oxford, Marston, and Barton with Risinghurst)

TABLE I.—*Age and Sex Incidence*

Ages in Years:	Under 1	1	2	3	4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64
Males ..	3	3	12	8	7	41	16	4	1	5	6	4	4	3	1	2	1
Females ..	3	5	9	8	18	43	18	7	7	7	16	9	6	0	0	0	0
Totals ..	6	8	21	16	25	84	34	11	8	12	22	13	10	3	1	2	1
	76																
Culminative percentage	27·5					57·8	70·0	73·9	76·7	81·0	83·9	93·6	97·2	98·4	98·8	99·6	100

were on the east side of these rivers. Within each area there were definite local foci of heavy infection with many cases occurring in the same or adjoining streets and often in neighbouring houses. A spot map gives the appearance of a number of small local epidemics occurring within one large epidemic. This characteristic of local areas of high incidence was noted by Nichamin, while Metcalfe Brown *et al.* (1952) gave details of one very heavy local infection in Manchester.

The epidemic, which started in North Oxford, reached its peak in this area from September 10 to 23. The Barton with Risinghurst area had a smaller outbreak with a peak from September 24 to 30. Central Oxford and East Oxford were the next two districts to show

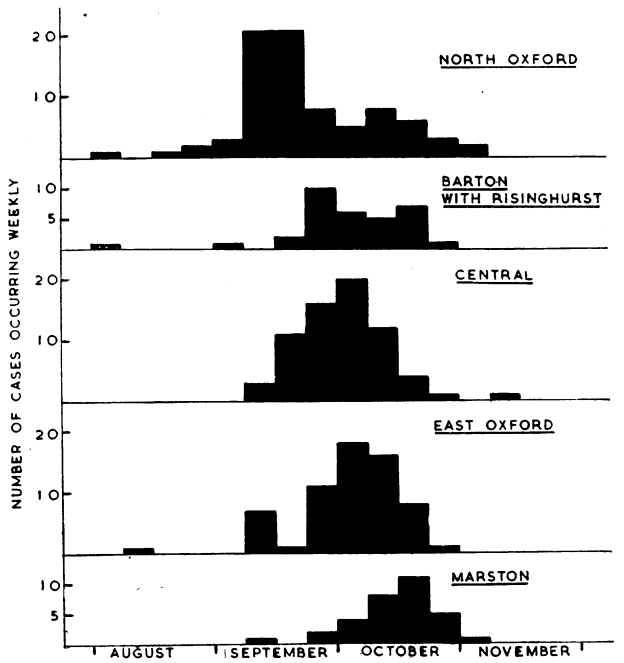

FIG. 2.—Weekly incidence of Bornholm disease in different districts of Oxford during August–November, 1951.

epidemic spread, each with peaks during the week October 1 to 7. Marston was the last district to be involved in the epidemic, and the peak incidence in this area was in the week October 15 to 21, which is at least four weeks later than the North Oxford peak. The incidence in these five areas is shown in Fig. 2.

There was a considerable similarity in the behaviour of the epidemic within each of these areas in that, after the occurrence of one or two sporadic cases, the outbreak rapidly built up to a peak and then quickly subsided. The epidemic on the Barton estate was of particular interest because the 23 cases all occurred in 11 different households concentrated in a small area of a new housing estate; the rest of the estate failed to produce a single case.

Characteristics of the Outbreak

Age and Sex Incidence.—Table I shows that the incidence was highest in pre-schoolchildren and young schoolchildren. Most cases occurred in the 4-year-old group, but there was a fairly uniform incidence at all ages from 2 to 9 years. There was a relatively high incidence amongst young married adults, and the impression was gained that this was predominantly a disease of young children and their parents. These findings are largely similar to those of Harder. Of the total group of 277 persons 121 were males and 156 females (ratio males to females 1 to 1.28). This small sex difference was present in most age groups.

Incubation Period.—In 89 patients the history of contact was definite enough for estimation of a probable incubation period. The results given in Fig. 3 show that 55 of the 89 cases (61.7%) had an incubation period of between two and five days, with the greatest number on the fourth day. Some cases had a longer incubation period, and there were several family outbreaks in which each victim appeared to have an incubation period from 9 to 13 days.

Density of Infection Within the Household.—Excluding single cases living on their own or cases in institutions, 255 have been classified as regards density of infection within the home. The results given in Table II are in agreement with those of Nichamin, who stated that in many instances only one member of a household was affected. The finding that 86 patients (33.6%) were single cases in a household suggests that, while the occurrence of multiple cases makes diagnosis easier, any apparent absence of spread should obviously not exclude the possibility of Bornholm disease. Not unnaturally, it is homes heavily attacked which have attracted most attention in the past, but, in the experience of this epidemic, such heavy household infections are the exception rather than the rule. There was no evidence that the degree of infectivity varied during the epidemic, and heavily infected households occurred as frequently at the start as at the end of the outbreak. The special health visitor classified the

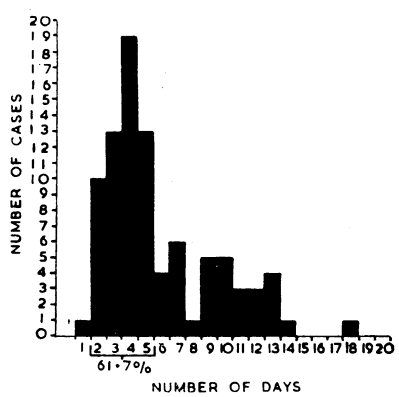

FIG. 3.—Incubation period.

TABLE II.—*Density of Infection Within the Household*

3	households	contained	5	cases	each
10	,,	,,	4	,,	,,
18	,,	,,	3	,,	,,
30	,,	,,	2	,,	,,
86	,,	,,	1	,,	,,

infected households, first, according to cleanliness, and, secondly, according to overcrowding; but a careful survey of her figures does not suggest any connexion between the cleanliness or overcrowding of the home and the density of infection.

Duration of Illness.—The duration of illness was recorded in the 262 cases investigated, and in 194 of them (74%) it varied between one and seven days, with a four-day illness as the most usual. In 52 cases (19.9%) it lasted between one and two weeks, and in 16 persons (6.1%) the illness extended beyond two weeks, the longest attack being 35 days. A general tendency was noticed for the illness in young children to last a shorter time than in adults; for instance, 66.2% of children under the age of 5 years had an illness of from one to five days' duration, compared with 38.1% in those over the age of 21 years, but isolated cases of long illnesses occurred among all age groups.

Spread of Infection in Schools.—In only two day schools was there any evidence that spread of infection had occurred among the pupils, and no outbreak was reported from any of the several boarding schools in the city. In an infant school of 145 children, 25 cases occurred among the pupils and staff in the period September 14 to October 15. In the nursery class the teacher developed a moderately severe attack on September 26, but stoically continued teaching, and probably infected seven children in her class of 30, of whom four became ill on September 29, two on September 30, and one on October 1.

Symptomatology.—Diversity of symptoms in Bornholm disease has been stressed by many writers, but no subsequent description has equalled Sylvest's classic monograph, which, with the exception of meningitis, contains reference to all the known signs, symptoms, and complications. Of the early English reports that given by Pickles (1937) remains one of the clearest clinical descriptions. Recent reports have tended to stress particular symptoms, the chest physician naturally seeing those cases with predominant chest signs, and the general surgeon those with acute abdominal pain. It is important to realize that the symptoms of this disease are many and varied, and Table III, giving details of 262 cases, particularly demonstrates this point.

TABLE III.—*Incidence of Symptoms in 262 Cases*

Pain in Abdomen and Chest		
Abdomen only		138 (52·6%)
Chest only		52 (19·8%)
Chest and abdomen		49 (18·9%)
No pain in abdomen or chest		23 (8·7%)
Severe Headache		
Spasmodic	19	
Constant	28	90 (34·3%)
Type not specified	43	
Other Symptoms		
Vomiting		40 (15·2%)
Photophobia		31 (11·8%)
Shivering		30 (11·4%)
Sore throat		27 (10·3%)
Pain in limbs		18 (6·8%)
Neck pains		13 (4·9%)
Dizziness		11 (4·2%)
Delirium		7 (2·6%)
Paraesthesiae and hyperaesthesiae		4 (1·7%)
Complications		
Benign meningitis: Definite		7 (2·6%)
Benign meningitis: Probable		9 (3·4%)
Orchitis		3 (10% of adult males)
Relapses		
Early		52 (19·8%)
Late		23 (8·7%)
Both early and late		5 (2%)

Pain

Spasmodic pain was present in practically every case, and the character of this constant symptom did more than anything else to make a diagnosis possible. The pain experienced varied greatly from case to case, from a mild stab to an extremely violent pain often described as the worst the individual had ever experienced. In most patients the pain at one time or another became severe, and at the height of the pain some adults said they did not know how they were going to face more of it. During the painful part of the illness there was usually some underlying pain, with sudden exacerbations from time to time. This characteristic feature was seen in pains in the abdomen, chest, and neck, and also in some frontal headaches. Experience varied from case to case, but the most usual story was an exacerbation of pain lasting from 5 to 10 minutes, followed by about half an hour of relative relief. During this latter period adults usually lay still and appeared apprehensive, especially if the exacerbations were acute; children varied very much in their behaviour at this time; some played quite happily with toys, but some of those more severely affected would doze off between the most acute spasms, particularly when these occurred during the night, which was usually the case. Another characteristic of the pain was that movement aggravated it, although continuing exercise did not cause an increasing severity of pain as in intermittent claudication. Those taken ill whilst up and about found it was too painful for them to stand up straight, and many adopted a curious "hunched up" attitude with the shoulders and head bent forward. Breathing was painful in all those with chest pain and in a few of those with high abdominal pain, but if the patient lay very still for some time the pain on breathing diminished.

Patients did not find it easy to locate accurately the position of the pain, particularly at the beginning of an attack, the area being indicated usually by a hand rather than a finger. Many different terms were used to describe the pain, the commonest being a "stabbing pain," but a number referred to a constricting pain like a very tight band, particularly in the case of the lower chest or forehead.

It was usual for the maximum pain to be experienced at the start of the illness, but there were a few striking exceptions, mainly in adults, in whom, after a period of malaise and minor pains, really acute pain occurred about five to seven days after the onset. The pain experienced in a relapse was nearly always very much less than that in the original attack.

Usually, in any one patient, pain was experienced in only one part of the body, but in some cases the pain shifted from place to place. In a family outbreak the location and severity of the pain in one member of the family was no guide to what was likely to occur in other members of the family. For instance, in one family outbreak two members had abdominal pain only, one member had thoracic pain, and one member had headache and pains in the neck. The following information has been collected about the pain in different situations.

Pain in Abdomen and in Chest

Abdominal Pain.—Just over half the patients (138, or 52.6%) reported abdominal pain as the main presenting symptom. The actual location of the pain was epigastrium or hypochondrium, 59 (42.7%); umbilical, 42 (30.5%); right iliac fossa (R.I.F.), 17 (12.4%); umbilical, moving to R.I.F., 10 (7.2%); lumbar or suprapubic 10 (7.2%). More patients had pain on the right side than on the left, and no patient complained of pain in the left iliac fossa. It will be seen that, at some stage, 27 patients complained of pain in the R.I.F. (17 had pain in the R.I.F. from the onset and 10 had pain starting at the umbilicus and moving to the R.I.F.), and as many of these cases were children the differential diagnosis from acute appendicitis presented real difficulty. While it is obviously undesirable to remove a normal appendix unnecessarily, this is not nearly so serious as mistaking a case of acute appendicitis for one of Bornholm disease. A short period of careful clinical observation will usually suffice to differentiate the two conditions. During a spasm children often threw themselves about and drew their knees up. In two cases examined during a spasm of pain, tenderness was present over the area of the pain and spasm of the underlying rectus muscle was noted. There were significantly more children and fewer adults in this group, and probably, therefore, the duration of the illness tended to be shorter than in the sample as a whole.

Chest Pain.—About one-fifth (52, or 19.8%) of the patients experienced chest pain as their main symptom. Adults formed a relatively high proportion in this group—namely, 46.1% against 25.9% of adults in the main sample—and probably for this reason a tendency was noted for the duration of the illness to be longer than normal. This group contained many of the patients who had very acute pain. The location of the pain varied, and covered most areas of the chest; it was usually unilateral, and the lower right side was affected more often than any other region. A coarse pleural rub was heard in two cases, but only a few cases were examined in the acute phase.

Abdominal and Chest Pains Combined.—Both chest and abdominal pains occurred in 49 patients. In 23 of these cases abdominal and chest pains developed at the same time; in 17 the illness began with abdominal pain followed later by chest pain; whilst in 9 cases chest pain was followed by abdominal pain. The age distribution of this group approximated very closely to that of the sample as a whole.

Miscellaneous Group with Neither Abdominal nor Chest Pain

There were 23 cases (8.7%) which did not experience pain in either the abdomen or the chest. The diagnosis was made only by their association with a family infection with typical symptoms. In 12 cases severe headache was the main symptom; seven patients complained of short-lived generalized aches and pains together with pyrexia; three cases had malaise and pyrexia; and in one case vomiting was the main complaint.

Headache

Most patients had some degree of headache, but in many of the cases a relatively mild headache was quite overshadowed by the severe spasmodic pain felt elsewhere. In 90 cases (34.3%) severe headache was a prominent symptom. About half-way through the inquiry it was realized that two different types of severe headache were occurring. Before this division was recognized 43 severe headaches were reported, the remaining 47 being classified as follows:

1. A severe spasmodic headache which can best be described as a pain similar in character to that felt in the chest or abdomen. In all cases the pain was in the frontal region and was often likened to a tight band across the forehead. Although present all the time, it became more severe periodically. This type of headache was found in 19 cases, two of which also had photophobia.

2. An extremely severe constant headache, usually occipital but occasionally frontal, was reported in 28 patients. This headache occurred most often as a late symptom coming on after about four to seven days' illness. Photophobia accompanied the headache in every case, and in 16 cases neck stiffness was also present. The seven proved cases of meningitis came within this group.

Other Symptoms

Temperature readings were not obtained in all cases, but in those in which careful records were kept the temperature was almost invariably raised, a reading of 101–103° F. (38.3–39.4° C.) being the usual finding. The onset of severe spasmodic pain was usually but not invariably accompanied by a rapid rise in temperature, and in a few cases there was a time lag of a few hours between the onset of the pain and the rise in temperature. Characteristically, the temperature dropped to normal or near normal when the severe spasmodic pain ceased. In a number of patients rapid temperature changes occurred throughout the day. It was not unusual to find a reading of 101–103° F. (38.3–39.4° C.) in the morning and evening, but only 99° F. (37.2° C.) in the middle of the day.

There was a history of shivering in 30 patients, including five who had a well-marked rigor at the onset of the illness. It was rather surprising that the rapid temperature changes which characterized many of the illnesses were not more often accompanied by shivering attacks.

Sore throat was reported by 27 persons but was never severe, and in 24 cases it lasted only one day. The sore throat developed at varying times during the illness.

In 18 cases pains in the limbs were experienced; these usually accompanied attacks of typical severe spasmodic abdominal or chest pain, and, because of this, patients tended to have a rather hazy memory of the less severe pain in the limbs. In most cases the pain seemed to involve the whole of a limb rather than muscle groups, and this was particularly so with patients in whom the pain was constant. A few patients had typical spasmodic pain, and others described shooting pains down one or more limbs. Two patients developed severe cramps of the feet, which in one case were troublesome for three days.

All the 13 persons who had pain in the neck had typical spasmodic pain which appeared to be related mainly to the sternomastoid and trapezius muscles.

Two patients (one adult and one child) showed marked hyperaesthesia, which was situated over the same area as the characteristic pain. The adult was particularly sensitive to changes of heat and cold.

Two patients had paraesthesiae: one, a child who had "pins and needles" on both sides of the chest; the other, an adult who complained of a pricking sensation in the feet which gradually moved up to the waist and was succeeded by the onset of typical severe pain in the shoulders and abdomen. One woman said her hands and feet felt as if they were swollen, although this was not so.

The dizziness which was prominent in 11 persons accompanied a severe headache in each case.

Vomiting at some time in the illness was reported in 40 cases; it was usually brief and occurred most often either at the onset of acute abdominal or chest pain or at the same time as the very severe headache of a developing meningitis. In two adults vomiting was particularly severe. In one of these, in whom severe chest pain and coarse pleural rub were present, vomiting began on the third day and lasted for a week, and during this period was the most troublesome symptom. In the other case, which was one in a large family outbreak, vomiting occurred at the onset, lasted two days, and was the most prominent symptom. There was no difference in the incidence of vomiting between those with abdominal pain, chest pain, or both abdominal and chest pain.

Ill-defined Illnesses in Other Members of Household

Of the cases, 29 were associated with an ill-defined illness in another member of the household. These illnesses included unexplained short attacks of pyrexia and transient pains in the abdomen, chest, neck, or head. In all persons the attack was so short-lived or ill-defined that it was felt that a definite diagnosis of Bornholm disease was not justified. The occurrence of these cases does, however, provide some evidence of the probability that subclinical and atypical attacks were not uncommon.

Complications

Meningitis.—Benign meningitis or encephalitis as a complication of Bornholm disease has been reported by many writers (Huss, 1934; Howard *et al.*, 1943; McConnell, 1945); while Hamburger and McNeil (1947) commented on the coincidence of outbreaks of Bornholm disease and benign lymphocytic meningitis. In the outbreak described there were seven cases (2.6%) of proved benign meningitis (six children and one adult). Five of these developed on the fourth to fifth day, one on the eleventh day, and one on the thirty-fifth day. In four of these cases there were attacks of characteristic spasmodic abdominal pain at the onset of the illness; in two cases typical chest pains occurred early, whilst the remaining patient had both abdominal and chest pain. There were nine other patients who had severe headache of a constant nature, together with photophobia and neck rigidity; in these no lumbar puncture was performed. It seems not unlikely that they were also cases of benign meningitis. This would make a total of 16 cases of meningitis (6.0%), a figure in close agreement with that given by Howard *et al.* In all

cases the meningitis was benign and full recovery followed, although in a minority there was a tendency to recurrent headaches.

Orchitis.—Three out of 30 adult males developed orchitis as a late complication (two on the fourteenth day and one on the fifteenth day). None of these gave a history of contact with mumps and none had any symptoms at all suggestive of mumps. In two cases the orchitis was bilateral. All subsided after three to four days.

Relapses and Sequelae

Relapses were a characteristic feature of this epidemic and could be divided into early relapses, occurring a few days after the acute attack, and late relapses, developing after at least one month's complete freedom from all symptoms. Altogether 80 patients (30.5%) experienced relapses—a figure in close agreement with that of Sylvest, who found that about one-fourth of his cases developed relapses. In the Oxford epidemic 52 (19.8%) persons developed early relapses, 23 (8.7%) late relapses, and 5 (2.0%) had both early and late relapses.

Early Relapses.—Typically, after a short illness the patient would suddenly improve and perhaps return to school or work, and then, after a further day or so, would just as suddenly become ill again either with the original symptoms or with new ones. Several patients had more than one relapse, and it was in this group that the most severe cases of the disease were found. The tendency for multiple relapses to occur made the patients very depressed. In a little more than half of the relapses the site of the pain was similar to that in the original attack, while in the remainder it was different. Fever was invariably present during a relapse. The condition of the patient during the improved phase before a relapse gave no indication that a relapse might occur, and at no time during the outbreak was it possible to forecast whether a relapse was likely in any individual nor what form a relapse would take.

Late Relapses.—Follow-up visits were made on 245 patients four to six months after the initial attack, and 28 gave a history of a further attack of typical pain after having been free from all pain for at least one month. Only 5 of the 28 patients had already had an earlier relapse. Most of the late relapses occurred between one and three months after the original attack, but the interval in one case was six months. These late attacks developed as suddenly and unexpectedly as the original ones, and in all of them the site of the pain was the same as that of the initial attack. In this respect the late relapses were different from the early ones. The pain in the late relapses was usually quite characteristic, so that the patient nearly always recognized it as identical with his original attack. In all late relapses pain was accompanied by fever. All age groups developed late relapses, which also occurred as commonly in those with abdominal, chest, or abdominal and chest pain.

Sequelae.—In 22 people (8.4%) after-effects of tiredness and weakness, with occasional muscular pains, were specially noted, but this does not indicate the true amount of debility generally felt by patients. Tiredness, loss of weight, and poor appetite were commonly reported in children, even in those in whom the attack had lasted only one to two days. In many children the debility following the disease appeared to be out of proportion to the severity of the initial attack, and many parents remarked how "run down" their children seemed to be.

Diagnosis and Prognosis

There is no doubt that a fuller knowledge of Bornholm disease by the general practitioner will often lead to a confident diagnosis in an otherwise puzzling and worrying case. At present, diagnosis must rest solely on clinical observation, and recognition of the characteristic spasmodic pain is the most useful single aid. The site of the pain, temperature changes, relapses, and all the other possible signs and symptoms must receive consideration, but are very variable. Laboratory aids to diagnosis are not yet available, and until the various types of Coxsackie viruses which are thought to cause Bornholm disease are clearly defined little help can be expected from the laboratory.

Distinct caution should be exercised regarding the immediate outlook because of the occurrence of unexpected relapses. Marked debility was a feature in some cases, with only gradual return to normal health, but the ultimate prognosis is good and the disease appears to have no mortality.

Treament and Prevention.—Treatment was symptomatic, and no specific means for prevention were taken.

Laboratory Investigations

Several instances have been reported of an association between Bornholm disease and the Coxsackie group of viruses (Curnen *et al.*, 1949; Curnen, 1950; Weller *et al.*, 1950; Findlay and Howard, 1950; Thélin and Wirth, 1951), and it is possible that a virus of this kind may be the causal agent of this disease.

In the Oxford epidemic, specimens of faeces taken on the first to seventh day after the onset from each of 17 patients with a diagnosis of Bornholm disease were tested for the presence of virus of Coxsackie type. In 11 instances no virus could be found, but in the remaining six cases viruses pathogenic for infant mice were recovered. In addition, five specimens of cerebrospinal fluid, one specimen of blood, and one throat swab were also tested, but attempts to isolate the virus from these sources failed. Three of the cases from which virus was successfully isolated occurred in the last week of September, which was the week immediately before the peak of the epidemic; two further isolations came from specimens taken during the second week in October—namely, the week following the peak of the epidemic; and the remaining isolation was from a specimen taken in the first week of November—that is, at the tail-end of the epidemic.

Technique of Isolation of Virus

Faecal specimens were prepared for inoculation by the technique given by Melnick *et al.* (1949). A 20% suspension was made by grinding the material in a mortar with phosphate-buffered physiological saline (*p*H 7.2) containing 10% normal inactivated rabbit serum. This was centrifuged at 2,750 r.p.m. for 15 minutes, and the clear straw-coloured supernatant fluid extracted overnight with one-third of its volume of ether. The water layer was then pipetted off and the ether removed under vacuum; penicillin and streptomycin were added to give a final concentration of 1,000 units and 1 mg. per ml. respectively. Suspensions prepared in this way showed no bacterial colonies when cultured on blood-agar plates. One litter of mice, not more than 48 hours old, was inoculated with each specimen by the intramuscular route. The size of the dose was 0.03 ml., and mice were observed for three weeks before being discarded.

TABLE IV.—*Virus Isolations from Faeces*

Case	Day of Disease Faeces were Taken	Isolation*	Passage Number		
			1	2	3
D. C. (Virus I) ..	3	5/8	8/8	8/8	5/5
L. D.	7	5/5	2/7	3/4	N.D.
R. D.	6	5/5	2/7	3/4	,,
A. McL. (Virus II)	2	6/6	4/4	4/4	10/10
P. D. S.	2	6/6	3/4	4/4	N.D.
S. S.	6	4/5	8/8	N.D.	,,

* Numerator = number of mice infected; denominator = number of mice inoculated.
N.D. = Not done.

The details of the virus isolations are given in Table IV. Two of the viruses isolated were studied in further detail. Both produced obvious signs of illness in infant mice, followed by death, and both could be serially propagated by means of suspensions of mouse carcasses which were bacteriologically negative. The first strain (Virus I) had in its fourth passage an LD_{50}, determined by the injection of serial

tenfold dilutions into five one-day-old mice per dilution of $10^{-7 \cdot 2}$. The LD_{50} of the second strain (Virus II) was $10^{-6 \cdot 9}$. The two strains differed in incubation period, Virus I having an incubation period of four days in mice of this age, while that of Virus II was two days.

Both viruses caused lesions in the brains and viscera of young mice. The lesions included inflammatory and degenerative lesions of the brain, myositis, lesions of the fat pads between the shoulder-blades, myocarditis, and signs of damage to the liver as described by Godman *et al.* (1952). These lesions are all typical of those caused by Coxsackie viruses of Dalldorf's histological Group B (Gifford and Dalldorf, 1951), and in other respects our viruses also resemble them. Both kill mice readily up to the tenth to twelfth day of life; in older mice infection is sporadic, and mice more than 21 days old only occasionally succumb to inoculation by any route. Pappenheimer *et al.* (1951) found experimentally that injection of Coxsackie virus Group B, antigenic type 1 (Conn.-5) into older mice causes extensive lesions of the acinar tissue of the pancreas. This is also a characteristic of both the Oxford viruses, although they differ from Conn.-5 immunologically. However, two viruses isolated by Forrester and Tobin (1951) from cases of Bornholm disease did not cause pancreatitis in adult mice. Further study of the two Oxford viruses showed that they were of the same immunological type, and therefore they will hereafter be referred to as the Oxford virus.

Serological Tests

Paired sera taken in the acute and convalescent stage from each of 13 patients in which a definite diagnosis of Bornholm disease had been made were tested for the presence of neutralizing antibody against the Oxford virus. The technique of the neutralization test used was that of Melnick and Ledinko (1950). All sera were inactivated by heating to 56° C. for 30 minutes before use. Serum diluted 1/5, 1/50, and 1/500 was mixed with an equal volume of virus, so that each mouse dose contained 1,000 paralysing doses of virus, and serum diluted 1/10, 1/100, or 1/1,000. The serum–virus mixtures were allowed to stand at room temperature for one hour and were then put up individually in sealed tubes and stored at −70° C. in a carbon-dioxide-ice cabinet. Mice approximately 24 hours old were used throughout the test. Litters born on the same day were pooled and the animals redistributed at random. Five to eight mice were given to each mother and one such batch was injected intramuscularly with each virus–serum mixture. As mice became available the appropriate virus–serum mixture was removed from the ice-box, thawed, and injected.

The results obtained in the 13 cases in which paired sera were available are shown in Table V.

In eight cases the sera taken during the acute phase of the disease showed little or no neutralizing power against the virus, but the serum specimen taken two to three weeks later showed a high content of antibody compared with that present in the first serum. It will be noted that this group of cases contains two individuals (R. D., P. D. S.) from whom viruses were isolated.

TABLE V.—*Neutralization of Oxford Virus by Sera Taken from Cases of Bornholm Disease*

Case	Serum Antibody Titre		Type of Antibody Response
	Acute Serum	Convalescent Serum	
E. B.	<10	100	+
R. C.	<10	100	+
R. D.*	<10	1,000	+
P. D. S.*	<10	1,000	+
M. S.	<10	100	+
P. R.	10	1,000	+
R. W.	10	1,000	+
J. L.	10	1,000	+
L. D.*	100	100	−
J. S.	1,000	1,000	−
A. McL.*	100	100	−
S. S.*	1,000	1,000	−
M. W.	1,000	100	−
D. C.*	−	<10	
J. L.	−	100	
H. L.	−	100	

Serum antibody titres are expressed as the highest dilution of serum which will protect mice against 1,000 LD_{50} of virus.
* Cases from which virus was isolated.

The other five cases had high antibody titres in both sera. This group included three patients (L. D., A. McL., and S. S.) from whom viruses were isolated. It is interesting that a similar occurrence of high antibody levels in both sera was found by Cheever *et al.* (1950) in an epidemic of "non-paralytic" poliomyelitis in Worcester, Mass.

A further group of three sera taken from children convalescent after Bornholm disease were tested for neutralizing power against the Oxford virus. Two cases showed a significant antibody titre, whereas in the third even the lowest serum dilution failed to protect infant mice against infection with the virus. It is interesting that this last case (D. C.) was the patient from whose faeces the Virus I strain was originally isolated. Nevertheless, this virus was undoubtedly concerned in the epidemic, since a clear-cut rise in antibody against it could be demonstrated in 8 out of 13 cases.

The findings place the viruses isolated from the Oxford epidemic in Group B (Dalldorf, 1950), which also includes those viruses which have been shown in the United States to be associated with epidemic myalgia. Preliminary cross-neutralization tests have been performed, using the Conn.-5 strain of virus—a strain of type B1 (Melnick *et al.*, 1949)—and the Oxford virus. Antisera against both viruses were prepared in hamsters by the technique described by Sickles and Dalldorf (1949). The results show that the Oxford virus does not belong to the same immunological type as the Conn.-5 virus. An epidemic of pleurodynia in the State of Washington studied by Lazarus *et al.* (1952) was associated with a virus of Group B antigenic type 3. Further tests are in progress to determine whether the Oxford virus corresponds to any of the four known antigenic types in Group B; but preliminary results indicate that it is not identical, although slight cross-reactions with type 1 may be shown by the use of high-titred antisera. Thus, while it is possible that Bornholm disease is always associated with Coxsackie virus of Group B there is now clear evidence that more than one immunological type of virus may be concerned.

Summary

A description is given of an epidemic of Bornholm disease which occurred among the general population of Oxford in the late summer and autumn of 1951. Detailed histories were obtained from 262 of the 277 cases traced.

The weekly rate of incidence rose rapidly to a peak in about four weeks and was followed by an equally rapid fall. Although cases occurred throughout the city, the epidemic was characterized by local areas of very heavy infection. The incidence was highest in young children. Spread within the family often occurred, but one-third of the cases were found to be single infections in a household. No connexion was found between cleanliness or overcrowding of the home and density of infection. Spread within schools was not a feature of the epidemic, but the experience of one infant school attacked is described.

The incubation period varied from 1 to 18 days, with the majority between two and five days. Symptoms were very diverse. The most useful single feature in diagnosis was the characteristic spasmodic nature of the pain. Pyrexia was usually present and severe headache was a common complaint. Other less frequent symptoms included vomiting, photophobia, shivering, sore throat, pain in the limbs or neck, dizziness, delirium, hyperaesthesiae, and paraesthesiae. In seven cases proved benign meningitis occurred as a complication, but the more probable figure was 16 (6%).

Orchitis was a complication in 3 out of 30 adult males infected. Relapses, both early and late, were a characteristic feature of the outbreak.

Viruses pathogenic for infant mice were isolated from the faeces of 6 out of 17 cases examined. Attempts to isolate virus from C.S.F., blood, and throat washings failed. The strain of Coxsackie virus isolated was identified as belonging to Dalldorf's Group B on account of the pathological lesions in mice. These included muscle, fat-pad, and cerebral lesions in infant mice, and extensive lesions of the acinar tissue of the pancreas in adult mice.

Paired acute and convalescent sera were obtained from 13 patients and tested for the presence of neutralizing antibody against the Oxford virus. A marked rise in neutralizing power in the convalescent serum was demonstrated in eight patients, whilst the other five cases had a high titre of antibody in both sera.

Preliminary cross-neutralization tests, using the Oxford virus, indicate that it may be a previously unrecognized antigenic type.

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An Australian tree, the Duboisia, has become an important source for the production of atropine and hyoscine. Before the last war the Duboisia was little more than a botanical curiosity, but when other sources of supply of these alkaloids were interrupted in 1940 Australian scientists found that the Duboisia leaf had considerable possibilities. A chemical processing method was developed, and soon the major requirements of the Allies were being met. Present exports of the leaf, although exceeding 100 tons a year, do not completely satisfy the demand. Steps are being taken to make good the heavy inroads on the natural growth of the trees during the war. It has been shown that commercial yields of more than half a ton of dry leaf per acre are possible.

BORNHOLM DISEASE IN CHILDREN

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Now that one or more strains of the Coxsackie virus have been shown to be involved in Bornholm disease (Curnen *et al.*, 1949; Shaw *et al.*, 1950; Findlay and Howard, 1950), it should be possible by virus sampling to delineate more clearly the clinical features of the condition. Although the earlier literature suggested that Bornholm disease bred true to type, it has been suggested that "benign lymphocytic meningitis" (Macdonald *et al.*, 1937; Dummer *et al.*, 1937), encephalitis (Howard *et al.*, 1943), and pneumonitis (Hopkins, 1950) may be superimposed upon pleurodynia. From virus studies it appears that at least three other syndromes have been described as due to the Coxsackie infection—non-paralytic poliomyelitis (Dalldorf and Sickles, 1948), herpangina (Huebner *et al.*, 1951), and three-day fever (Webb and Wolfe, 1950). On the question of whether one strain of virus can give rise to several different syndromes, the evidence is inconclusive, though Bury and Tobin (1952) suggest that it can.

During the 1951 Bornholm epidemic in Great Britain 104 children with the clinical appearances of Bornholm disease were admitted to Dudley Road Hospital, Birmingham. This communication describes the clinical features of these typical cases and reports the results of a search for the Coxsackie virus among them; it also discusses the virological findings in 26 atypical cases which had clinical features differing slightly from true Bornholm disease but which for various reasons were thought possibly to be related.

Typical Cases

We have taken the following features as necessary to make the diagnosis: pain in muscles, usually of chest or abdomen; brief or recrudescent course, absence of demonstrable pulmonary or other lesions; and occurrence in epidemic form. We have therefore excluded all cases showing definite radiological changes in the chest.

The Epidemic.—On June 2, 1951, a girl aged 13 was admitted to the ward with a history of sharp stabbing pain in the right side of the chest for the past 18 hours. Although there were no abnormal chest signs she was treated as a case of pneumonia with penicillin and a sulphonamide. Next day she was much improved; the temperature was normal and the chest *x*-ray film clear, and the diagnosis of Bornholm disease seemed more likely than the original one of pneumonia. In the next few days further similar cases showed that we were in the midst of an epidemic, while retrospective examination of notes led us to discover a further six cases which had been labelled pleurisy, pneumonia, P.U.O., and the like. On June 12 one of us was asked to see a boy of 7½ who had been admitted to a surgical ward on June 9 with one day's history of sharp stabbing pain in the upper abdomen, nausea, and anorexia. His case was similar, and it caused us to take an interest