himself. Like all boundaries, and like this boundary line outside, this parallelism contains the possibilities of friction; but, what is more important, it affords an irreplaceable instrument of discussion and mutual comprehension, which is even more valuable than the tendering of expert advice and technical information. This instrument depends for its effectiveness upon the medical profession inside the Departments being as perfectly as may be in tune with the profession outside and as fully representative and characteristic of the profession's outlook and mind as can be devised. I will not here enter into the various ways in which this condition can be maintained and guaranteed, but will content myself by saying that the politician has good reason to be zealous and grateful for it.

Self-analysis is an exercise to be indulged in sparingly, especially in public. This evening I have gone further still, and ventured upon a joint self-analysis of my own profession and another, at least of their points of contact and connexion. I have essayed it only because I believed that such analysis might contribute something to the mutual understanding and co-operation on which the success of the National Health Service is conditional.

OUTBREAK OF E.C.H.O. TYPE 9 INFECTION IN A CHILDREN'S HOME

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During the summer of 1959 outbreaks of febrile illness in children were reported in the *British Medical Journal* from areas as far apart as Glasgow, by Landsman *et al.* (1960), and Much Wenlock, Shropshire, by Parton (1960). The Glasgow outbreak was found to be caused by E.C.H.O. type 9 virus, and, although no specimens were examined in the Much Wenlock incident, the medical syndrome there seemed to be very similar to that described in Glasgow. There have been several reports of E.C.H.O. 9 virus causing "aseptic meningitis" in members of the same family. Rotem (1957) tabulated the number of cases occurring in families and found that the highest incidence in one family was five cases. Two or more cases in 25 houses were found by Garnett *et al.* (1957) in a survey carried out during an epidemic in East Suffolk.

In August, 1960, a number of residents in a children's home in Edinburgh developed a febrile illness, and the causative organism was found to be E.C.H.O. 9 virus. This outbreak in a closed community gave an opportunity to study some of the epidemiological features of this virus infection. It was found that out of a total of 27 children resident in or closely connected with the home 17 showed clinical signs of infection, and out of 10 adults connected with the home only 2 were affected.

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History of Outbreak

A 5-year-old boy, living in a residential children's home, complained of abdominal pains during the forenoon of August 11; at noon his temperature was 102.6° F. (39.2° C.) and he had developed neck stiffness. Next morning his temperature was normal, but his tonsils were inflamed. The following morning, the third day, he started vomiting. By noon his temperature had risen to 103.8° F. (39.9° C.), he showed signs of meningeal irritation, and he was transferred that afternoon to the Edinburgh City Infectious Diseases Hospital. He was diagnosed as a case of "aseptic meningitis," and E.C.H.O. 9 virus was later isolated from his stool, but not from the cerebrospinal fluid, which was also examined.

On the same day, the third day, a 5-year-old girl developed a severe frontal headache and her temperature was found to be 101.2° F. (38.4° C.). From the third to the eighth day, a period of six days, 13 children were similarly affected; thereafter the number of cases diminished, and from the ninth to the sixteenth day three more children and two adults were affected.

The most common presenting symptom was abdominal pain—11 out of 17 children being affected this way; of these 11, 4 also complained of severe frontal headaches. Two young children, aged 3½ and 2½, were diagnosed as cases because they were flushed and were found to have temperatures of 100.6° F. (38.1° C.) and 100.2° F. (37.9° C.) respectively. Apart from the initial patient, who was admitted to hospital, all the children were nursed in the home.

TABLE 1.—Presenting Signs or Symptoms

		0-4 Years	5-9 Years	10-14 Years	%
Abdominal pains only	Male	—	3	—	41.2
	Female	—	2	2	
Headaches only	Male	—	1	—	23.5
	Female	—	1	2	
Abdominal pains and headaches	Male	—	2	1	23.5
	Female	—	—	1	
Fever only	Male	2	—	—	11.8
	Female	—	—	—	
Total	Male	2	6	1	
	Female	—	3	5	

Temperatures were recorded twice daily when the symptoms or signs (shown in Table 1) were notified, and in each case it was elevated, the average being 100° F. (37.8° C.). The acute stage was deemed to be terminated when two successive normal temperatures were obtained, and this took place at a minimum of two days to a maximum of six days after onset of symptoms, with an average of four days. During this acute phase a few other signs and symptoms were noted. Vomiting occurred in nine cases, seven during the third day of illness and two during the fourth day. Four children who had vomiting also complained of neck pains. The first patient also complained of a sore throat, and one girl, aged 14, developed on her face, neck, and trunk a faint reddish-pink blotchy rash, which lasted two days.

Even when a normal temperature was attained the children had not fully recovered; they were left with a general feeling of lassitude, and it took on the average two to three weeks for them to regain their normal health. In two cases there was a subsequent rise in temperature. In a 3½-year-old boy the temperature was

normal both in the morning and in the evening of the fourth day, but on the fifth it had risen to 102° F. (38.9° C.) and on the sixth was 100.4° F. (38° C.); it was back to normal, where it remained, by the evening of the sixth day. A 14-year-old girl whose temperature was normal by the fifth day developed a frontal headache on the sixth day and her temperature was found to be 101° F. (38.3° C.). On the ninth and tenth days her temperature was back to 98.4° F. (36.9° C.), but on the eleventh day it had risen to 100.8° F. (38.2° C.) and she was again complaining of frontal headache and also of neck pains. Next day the temperature was normal and remained so.

In addition to the children resident in the home there were in close contact with them a matron, an assistant matron, a children's nurse, a cook, a young resident maid, two women employed as cleaners, who came in during the mornings, and a lodgekeeper and his family. The lodgekeeper helped with odd jobs in the house, as did his wife. Their daughter was employed in the home as a second children's nurse, and their 9-year-old son played with the other children.

The son was one of the 13 children who fell ill between the third and eighth days—that is, during the period when the bulk of the cases occurred. The daughter, aged 18, complained of severe frontal headache, neck pains, and sore throat on the twelfth day and her temperature was found to be 102° F. (38.9° C.). Four days later, on the sixteenth day, the lodgekeeper's wife complained of severe frontal headaches, abdominal pain, and sore throat, and her temperature was found to be raised. Also at home during this period was the lodgekeeper's other son who was on leave from the Army, but neither he nor his father was affected.

The Chart shows how the number of cases, children and adults, were distributed over the 16 days of the outbreak.

The children resident in the home itself have been further tabulated according to their sleeping accommodation.

TABLE II

	Infant Room	Boys' Room	Girls' Room	Older Girls' Room	Single Room
Affected	6	3	4	2	1
Not affected	1	6	2	1	—

Out of the 17 children affected, analysis showed that 11 (out of 14) were in the 1-9 age-group as compared with 6 (out of 12) in the 10-14 age-group. However, these numbers are too small for us to be able to detect a significant difference in the age incidence of ill children and therefore no conclusions could be drawn.

The clinical findings of Jamieson *et al.* (1958) are similar to those mentioned here. They found that the main features were pyrexia, headache, and vomiting. Temperatures were found to range between 100 and 102° F. (37.8° and 38.9° C.), but the average duration of pyrexia (seven to eight days) was longer than in the present series. Garnett *et al.* (1957) described three essential symptoms—very intense headache, vomiting, and fever, with pyrexia lasting up to four days.

Action Taken

By the fourth day of the outbreak there were seven children affected, one of whom had been removed to hospital. It was decided with the matron that no visitors were to be admitted into the home and no children were to be allowed out visiting. Fortunately at this time the schools were still on holiday, and this probably prevented a more widespread outbreak, because the children were spread over three different schools. It was also agreed that the children should not be allowed back to school until a period of two weeks had elapsed after the last case. This meant that the children missed the first three weeks of the new school session.

The home had sufficient accommodation to enable children who developed signs of infection to be transferred from their own sleeping-quarters to temporary sick-quarters which were placed out of bounds to other children.

Finally, roller towels which were used in the home were replaced by the more hygienic disposable paper towel in order to cut out one possible source of person-to-person transmission of the virus.

Laboratory Investigations

Examination of Faeces

Samples of faeces were collected in sterile 1-oz. (28-ml.) universal containers and transmitted to the laboratory on the same day. On receipt of the specimen about 2 g. of faeces was emulsified in 5 ml. of Hanks's solution containing 100 units of penicillin, 100 µg. of streptomycin, and 25 units of nystatin per ml. After centrifuging for 15 minutes at 3,000 r.p.m. the supernatant fluid was withdrawn and allowed to stand at room temperature for four to six hours.

The monkey-kidney-tissue cultures used in this investigation were obtained from two sources—the Medical Research Council Laboratories, Hampstead, and Glaxo Ltd. The cultures from the former were maintained in Hanks's solution plus 4% lactalbumin hydrolysate, 2% horse serum, 4% of a 4.4% solution of sodium bicarbonate, together with penicillin, streptomycin, and nystatin; cultures from the latter in synthetic medium 199 plus 2% horse serum, 2% of the 4.4% bicarbonate solution, and the usual antibiotics.

Inoculations of faecal suspensions were made in whichever type of culture happened to be available, each of two tubes receiving 0.1 ml. of suspension and 0.9 ml. of maintenance medium. The tubes were then incubated in a roller drum at 37° C. and examined on alternate days. Any culture showing cell destruction was passed into fresh cultures immediately; those exhibiting no change were rejected after 14 days as negative.

Cytopathic changes occurring in subcultures were regarded as being due to virus growth, and the

harvested fluids were submitted to neutralization tests in monkey-kidney cells in an attempt to identify the virus. These tests were performed with 100 TCD50 doses of virus against the three poliomyelitis antiserum types, and Coxsackie B1 to 6, obtained from the Standards Laboratory, Colindale, and against E.C.H.O. types 1 to 14 obtained from Microbiological Associates, Bethesda, U.S.A.

Since most of the Coxsackie A viruses do not infect tissue cultures all the faecal specimens from which no cytopathic agent was isolated were inoculated by the subperitoneal and intracerebral routes into suckling mice less than 24 hours old. The litters were examined daily for three weeks for signs of paralysis or muscle weakness, the absence of which was taken as evidence of a negative result.

Serum Antibody Tests

On receipt of the venous blood samples the serum was separated and stored at -30°C . until required for titration. When it became evident that E.C.H.O. 9 was the only virus to be isolated from the faeces, serum antibody titrations were performed on all specimens by the neutralization method in tissue culture, using an infecting dose of 100 TCD50 of an E.C.H.O. 9 virus previously isolated in this laboratory. Any serum giving a positive result in a preliminary screening test at a dilution of 1 in 4 was thereafter fully titrated.

Results

Specimens of faeces were obtained during the acute phase of the illness from all of the 19 individuals who developed symptoms and signs of infection. E.C.H.O. 9 virus was isolated from 10 of the 17 children, including the boy admitted to hospital. The same virus was isolated from the faeces of the lodgekeeper's wife and daughter, although in the latter case it was the second specimen that yielded the virus, the first having proved negative. No virus was isolated from first or second specimens from the lodgekeeper's sick son.

Stools were also obtained from 11 persons who were not ill. These were the matron, assistant matron, cook, children's nurse, maid, one of the cleaners, the lodgekeeper, and four children. From none of these cases was virus isolated.

From all those who had been ill a second specimen of faeces was collected two weeks after the temperature had subsided. Only 2 of the 10 children originally positive were still excreting virus; in a further two weeks, when a third specimen was obtained, one of these became negative. A fourth specimen taken from the remaining positive case nine weeks after onset of the illness gave a negative result. The lodgekeeper's wife and daughter had positive stools for periods of eight weeks and nine weeks respectively. The results obtained from examination of the faeces are shown in Table III.

TABLE III.—Examination of Faecal Specimens

	Ill	Virus Isolated	Not Ill	Virus Not Isolated
Boys	9	4	2	2
Girls	8	6*	2	2
Adults	2	2†	7	7
Total	19	12	11	11

* Second specimens also positive in two cases.

† Second specimen positive in one case, second and third specimens positive in the other.

Serology

It was not possible to collect sera from all the patients, but specimens were obtained from 12 of the 17 ill children, from the lodgekeeper's wife and daughter, and from the cook, who was not ill. Second specimens proved even more difficult to obtain, but four were collected after an interval of three weeks from two of the children, the lodgekeeper's wife, and the cook.

Serological tests were performed on 14 of 19 who were clinically ill, and all of these revealed high titres or rising titres. All the 10 cases from whom virus was isolated showed significant antibody levels. Of the seven patients from whom no virus was isolated, serum specimens were taken from four, and all of these had neutralizing antibody titres ranging from 1 in 64 to 1 in 256.

Sera and stool specimens were also obtained from two children who exhibited minimal clinical signs. One of these, a boy of 10, developed headache and abdominal pain one afternoon, at which time his temperature was 98.6°F . (37°C .), but next morning he had no symptoms and his temperature was normal. The other was a girl of 9 who complained of abdominal pains and whose temperature was found to be 98.6°F . (37°C .). On the morning and evening of the following day the temperature was 99.2°F . (37.3°C .), but by the next morning it had returned to normal. These cases are incorporated in Table IV.

TABLE IV.—Examination of Sera for Antibodies to E.C.H.O. 9 Virus

	Age	Virus in Faeces	Reciprocal Titres	
			1st Serum	2nd Serum
Boys { 1*	5	+	16	256
	2	+	256	256
	3	—	64	No specimen
	4	+	64	"
Girls { 1	11	+	256	"
	2	+	16	"
	3	+	128	"
	4	—	128	"
	5	+	128	"
	6	+	64	"
	7	—	256	"
	8	+	256	"
Adults { 1	49	+	8	64
	2	+	256	No specimen
	3†	—	<4	<4
	57	—	<4	<4
Boy ‡	10	—	<4	<4
Girl ‡	9	—	16	16

* Admitted to hospital. † The cook, who was not ill. ‡ The children who exhibited minimal clinical signs.

Antibodies were not demonstrated in the paired sera from the cook, who was not ill and from whose faeces no virus was isolated. It was discovered that prior to the first case occurring in the home the cook was the only adult who had had any form of illness. This had taken the form of epigastric pains and puffiness of the face, coming on after eating tinned sardines, and was regarded as an allergic manifestation. Her doctor prescribed an antihistamine drug, to which the condition quickly responded, further suggesting that it may have been an allergy.

Discussion

An outbreak of an enterovirus infection in a children's home gave us the opportunity to study the infectious nature of this condition and also to carry out laboratory investigation in a relatively closed community.

No doubt there were a number of children in the city during the summer months who had mild attacks of abdominal pain, with perhaps frontal headache, and,

because they seemed to recover in two or three days, had their symptoms attributed by parents to some dietary indiscretion. The fact that so many children in this home fell ill in so short a time, immediately suggested that this outbreak was of an infectious nature. During a period of 16 days 19 cases occurred, 13 of them in the space of six days, but an accurate incubation period cannot be deduced from these figures. So far as the children were concerned, the numbers were too small to detect whether age or sex was associated with susceptibility to the virus.

Roller towels were in use by the children, and it is possible that the infection was transmitted in this way. The adults, on the other hand, had their own toilet and washing facilities and so were less liable to this form of contamination. The two adults who were affected were mother and daughter, and the young son of this family was also a case. It is therefore a possibility that transmission could have taken place via a towel, W.C. seat, chain-pull, etc., in this house. On the other hand, the father and other son, who were also similarly exposed, were not affected.

Examination of stool specimens suggested that on the average the period of infectivity ceases a fortnight after the patient becomes afebrile, although the two adults affected remained positive for eight and nine weeks respectively after clinical defervescence. With such small numbers it is impossible to state categorically that adults remain positive excretors for longer than children.

Summary

An outbreak of an enterovirus infection in a children's home is described.

Of a total of 27 children, 17 showed clinical signs of infection; and of 10 adults connected with the home two were affected. The 19 cases occurred in a 16-day period, 13 of them within the space of six days.

The most common presenting symptom was abdominal pain, although frontal headache, alone or associated with abdominal pain, was fairly common. The average temperature was 100° F. (37.8° C.) and the duration of pyrexia ranged from two to six days.

E.C.H.O. type 9 virus was isolated from the faeces of 12 of the 19 subjects who developed clinical illness. Serum from 14 of the 19 cases was examined, and antibodies were present in all 14.

We thank Professor R. Cruickshank, bacteriology department, Edinburgh University, and Dr. H. E. Seiler, Medical Officer of Health, Edinburgh, for their encouragement and advice. We are indebted to Dr. H. C. Duncan, medical officer in charge of the children's home, for allowing us to carry out this investigation, and to the matron and staff of the home for their co-operation. We are especially grateful to Miss A. Anderson for technical assistance and to Dr. J. M. Mair for criticism of the manuscript.

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EXPERIMENTAL STUDIES ON THE PREVENTION OF Rh HAEMOLYTIC DISEASE

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ABO Incompatibility

In the context of haemolytic disease of the newborn, ABO incompatibility means that the father's blood is unsuitable for transfusion into the mother, and our interest in this stems from the work of Levine (1943), who noted a deficiency of such mating types in the parents of affected children. He deduced, therefore, that ABO incompatibility affords a degree of protection against Rh haemolytic disease, and this has been confirmed by many workers. Of particular interest are the experiments of Stern *et al.* (1956), who showed that male volunteers could be much more easily sensitized to Rh if the injected blood were ABO compatible.

Nevanlinna and Vainio (1956) emphasized the importance of the sensitizing foetus and showed by means of a family study that once sensitization had occurred there was no evidence that ABO incompatibility between mother and foetus afforded any further protection. We carried out a somewhat similar survey in order to determine the ABO group of the Rh-sensitizing foetus, and in 14 ABO incompatible matings in which the sensitizing foetus could be determined with certainty its ABO group was always compatible with the mother (this can happen because of heterozygosity in the father—for example, a group O woman married to an AO man can produce a group O child). The probability of our results being found by chance alone was less than 1 in 500 (Clarke *et al.*, 1958). Nevertheless, the sensitizing foetus is not invariably ABO-compatible, and we have recently found one which is incompatible.

One of us (R.F.) has investigated a series of 85 families with Rh-negative mothers where four or more children have been born and yet no haemolytic disease or Rh sensitization occurred. In 22 the husband was also Rh negative, but in the remainder the percentage of ABO incompatible matings was 42.9% $\pm$ 6.23 compared with 33.6% in the general population (as judged by phenotype frequencies) and 22.0% $\pm$ 2.83 in the investigated families with haemolytic disease (Finn, 1961).

The most obvious explanation for the protection afforded by ABO incompatibility is that suggested by