The most promising field in respect to tobacco at present appears to be further research to identify the carcinogens in tobacco smoke and to reduce the exposure to the carcinogens by effective filtration or modification of the tobacco in cigarettes, pipes, and cigars. If safer tobacco products can be developed—and current laboratory results are encouraging—then these can be substituted for present products. Such modifications might reduce the incidence of oral cancer and also the incidence of lung and larynx cancer and other cancers related to smoking. Another measure which can be begun now would be the health education of students in high school. One preventive measure, in conjunction with alcohol effects, would be improved nutrition, particularly with respect to possible supplements of iron and vitamins B and C.

These recommendations apply primarily to oral cancer in countries such as the United States. Preventive measures have to be tailored to the particular situation, and therefore the emphasis in other countries might be somewhat different. In Sweden, for example, current preventive measures in respect to dietary supplements are already achieving a reduction in Plummer-Vinson disease, and, we believe, will eventually reduce the incidence of oral cancer in women from Northern Sweden. In India, moderation in the use of bidis and betel-nut chewing should lead to a great reduction in oral cancer. In the warmer regions of the globe protection against excessive exposure to sunlight, particularly among fair-skinned people, represents a preventive measure for lip cancer.

From the point of view of preventive medicine we can avoid many of the semantic tangles and arguments that have hampered the study of environmental agents in cancer. The important question is not whether an agent is "associated with," "increases the risk of," "causes," "initiates,"

or "promotes" cancer at a given site, although this question is of academic interest. The essential question is whether control measures can be devised which will reduce the incidence of the cancer. Similarly, we can avoid the confusion engendered by multiplicity of factors. A disease such as cancer has a complex aetiology, and,

FIG. 9.—Aetiological factors in cancer of the oral cavity.

as this study indicates, there may be many factors operating (Fig. 9). Even if a given factor accounts for a few cases, this is surely no reason to ignore factors which account for the majority of the cases. The viewpoint of preventive medicine enables us to maintain some perspective and to keep us from focusing all of our attention on a handful of highly interesting but very rare case histories.

Finally, we would like to make clear the spirit in which these predictions and recommendations are made. We cannot claim that some assertions are absolutely correct, since they have not been subjected to the final test of experience. Until control measures actually reduce the incidence of disease, we can only employ indirect arguments. The final proof of epidemiological data, however, the reduction of disease, cannot be accomplished until proper control measures have been instituted.

The goal we expect to attain demands that we give this problem our fullest attention. If our conclusions are correct, then perhaps much of the suffering and death from oral cancer can be avoided. We do not believe, as stated at the onset of this discussion, that the development of practical control measures must await a complete understanding of the pathogenesis of a given disease. This holds

as true to-day as it did during the days of Snow. In this concept lies the practical significance of epidemiological research and preventive medicine.

REFERENCES

- Haenszel, W., and Shimkin, M. B. (1956). *J. nat. Cancer Inst.*, **16**, 1417.
 Jellinek, E. M., and Jolliffe, N. (1940). *Quart. J. Stud. Alcohol*, **1**, 110.
 Khanolkar, V. R. (1950). *Acta Un. int. Cancr.*, **6**, 881.
 Martin, H. E., Munster, H., and Sugarbaker, E. D. (1940). *Arch. Surg. (Chicago)*, **41**, 888.
 Moore, G. E., Bissinger, L. L., and Proehl, E. C. (1953). *J. Amer. Geriatr. Soc.*, **1**, 497.
 Public Health Service, Federal Security Agency (1950-2). *Cancer Morbidity Series*, 1-10 (Public Health Service Publ. No. 13, 65, 67, 112, 126, 152, 178, 216, 217, 244). Washington, D.C. Government Office.
 Sadowsky, Doris A., Gilliam, A. G., and Cornfield, J. (1953). *J. nat. Cancer Inst.*, **13**, 1237.
 Sanghvi, L. D., Rao, K. C. M., and Khanolkar, V. R. (1955). *British Medical Journal*, **1**, 1111.
 Wynder, E. L. (1957). In preparation.
 — Bross, I. J., and Day, E. (1956). *Cancer*, **9**, 86.
 — and Feldman, R. (1957). *Ibid.* In press.
 — Hultberg, S., Jacobsson, F., and Bross, I. J. (1957). *Ibid.* In press.
 — and Wright, G. (1957). *Ibid.* In press.

SEROLOGICAL EVIDENCE OF INFECTION WITH SENDAI VIRUS IN ENGLAND

BY

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The first description of Sendai virus as a possible cause of human disease was given by Sano *et al.* (1953), who investigated an outbreak of pneumonitis among newborn infants in a hospital at Sendai, Japan. Twelve out of 17 patients died. The onset was acute, with pyrexia, cyanosis, and marked dyspnoea. X-ray examination showed opacities in the lung fields of some cases, but there were few physical signs in the chest. Jaundice developed in a few cases. From five of the fatal cases, Kuroya *et al.* (1953) isolated a virus by the intranasal inoculation of mice with lung extracts and adapted it to grow in fertile hens' eggs. These workers also reported that a pyrexial disease with pneumonitis occurred in a human volunteer aged 8 years who had been inoculated intranasally with the virus and from whom it was subsequently re-isolated. Later the virus was found to have the property of agglutinating the red-blood cells of a fowl. Haemagglutination-inhibiting antibodies were found in the residents of the town of Sendai but were not present in residents of three other districts. The properties of this virus were also investigated in Japan by Fukumi *et al.* (1954).

In the course of a serological survey of sera from a variety of illnesses in the U.S.A., Jensen *et al.* (1955) found evidence of infection with Sendai virus in two patients; one had suffered from an atypical pneumonia and the other from a nondescript respiratory illness of two to three days' duration. No virus was isolated by these workers. They suggested that the virus might be termed influenza D.

Serological evidence of infection with Sendai virus was detected in this country in 1956 (Bruce White, Gardner, and Hope-Simpson, 1957), during the investigation of an outbreak of respiratory disease in a hospital for the chronic sick. Additional serological evidence of infection has been found in England in a number of other patients, details of which are the subject of this report.

Materials and Methods

For this investigation use was made of all suitably paired sera sent to this laboratory during 1956 from patients suffering

from respiratory disease. Only paired samples of serum consisting of one taken during the acute stage and one taken about ten days later during convalescence were judged suitable for examination by complement-fixation tests (C.F.T.).

The Sendai and mumps virus particle antigens were prepared as described by Bruce White *et al.* (1957), having been made from the same virus strains.

A total of 872 pairs of sera were examined for complement-fixing antibodies to Sendai and mumps virus particle antigen. These consisted of 615 pairs of sera examined for the routine diagnosis of respiratory disease and 257 sera collected at various Royal Air Force stations during a survey of respiratory illness. The R.A.F. sera were examined only for antibodies fixing complement with the antigens of influenza A and B, adenovirus, Sendai, and mumps (virus particle antigens); the remaining sera were tested with antigens of *Rickettsia burneti* and the viruses of influenza C and psittacosis, as well as the antigens used for the R.A.F. sera. A *Streptococcus M.G.* agglutination test for the detection of atypical pneumonia was carried out on the sera of cases sent to this laboratory for routine testing.

Case Reports

Serological evidence of recent infection with Sendai virus, as denoted by a fourfold rise in the titre of complement-fixing antibodies to Sendai virus, was found in 23 cases (4 children and 19 adults); the convalescent titres ranged from 1/8 to 1/64. The salient features of the histories of these cases are summarized in the accompanying Table.

Summary of Clinical History of Patients Suspected of Being Infected with Sendai Virus

Case No.	Age and Sex	Date of Onset	Respiratory Illnesses			History of Mumps
			With Pneumonia	Without Pneumonia	Laryngeal Symptoms	
1	79 M	19/1/56	+	—	—	N.K.
2	59 F	20/1/56	+	—	—	N.K.
3	79 F	3/2/56	—	+	—	N.K.
4	87 F	13/2/56	+	—	—	N.K.
5	90 F	13/2/56	—	+	—	N.K.
6	Ad. M	11/2/56	—	+	—	N.K.
7	21 M	9/2/56	—	+	—	N.K.
8	18 F	14/2/56	—	+	—	N.K.
9	20 M	14/2/56	—	+	—	N.K.
10	20 M	16/2/56	—	+	—	N.K.
11	34 M	21/2/56	—	+	—	N.K.
12	50 M	23/1/56	—	+	—	—
13*	2 M	11/4/56	—	+	—	—
14	8 F	28/3/56	+	—	+	+
15	6 M	27/9/56	—	—	+	—
16	8 F	2/10/56	—	—	+	—
17	49 M	12/11/56	—	+	—	+
18	Ad. F	20/11/56	—	+	—	—
19	51 F	24/11/56	—	+	—	N.K.
20	35 M	Late Nov. 1956	—	+	—	—
21	52 F	5/12/56	+	—	—	N.K.
22	58 M	10/12/56	—	+	—	N.K.
23	51 F	11/12/56	+	—	—	N.K.

Ad.=Adult. N.K.=Not known. +=Predominant feature. —=Minor or absent feature. * This patient also had conjunctivitis and a lymphadenitis.

Cases 1–6 occurred or were associated with an outbreak in a hospital for chronic sick (Bruce White *et al.*, 1957).

Cases 7–11 were single cases which occurred in R.A.F. stations and were not associated as an outbreak. Influenza A was prevalent in these stations at this time.

Cases 12–23 were cases of sporadic disease or family outbreaks in Southern England, from which sera were sent to the laboratory for routine diagnostic tests for respiratory infection. Cases 15 and 16 were brother and sister; Cases 17 and 20 occurred in the same doctor's practice; Case 23 occurred in the same town as the original outbreak in the hospital for the chronic sick. Some members of the families of Cases 6, 17, and 18 had a similar illness but no sera were available for testing.

The most severe illnesses were in those over 50, five of whom had pneumonia. Three of the children showed a predominance of laryngeal symptoms, such as hoarseness, loss of voice, dyspnoea, and stridor. All cases were characterized by an infection of the upper respiratory tract and in

most there were signs of a more general systemic infection. The only evidence available regarding the probable incubation period of this illness was obtained at the hospital for the chronic sick, where the technician (Case 6) was in contact with Cases 2 and 3 on the third day of their illness. If he acquired his infection from Case 3 the probable incubation period would be about five days, if from Case 2 about 19 days.

Discussion

When both Sendai virus and influenza virus A infection were occurring together, as in the R.A.F. and in the hospital for the chronic sick, no clinical differences between the types of infection were apparent. Cases of Sendai virus infection were detected throughout 1956, although the majority occurred at the beginning and the end of the year. The apparent concentration of cases at the beginning of the year may be of no significance, as six cases were from one outbreak occurring in January and February, and five were in R.A.F. personnel from whom the sera were collected only during the five-weeks period February 10 to March 19.

During 1956, 96 of 615 pairs of sera tested, excluding those from the R.A.F., gave fourfold or greater rising titres positive to a variety of virus agents in the routine examination of sera from patients with pyrexia of unknown origin or infection of the respiratory tract. These consisted of 60 positive to influenza A, 16 to adenovirus, 2 to influenza C, 11 to psittacosis, and 5 to *Rickettsia burneti*; there were also two rising titres in the agglutination test with *Streptococcus M.G.* None of these had rising titres to Sendai virus. However, in Case 9, one of the R.A.F. series, there was a diagnostic rise in titres to influenza virus A (the titre for influenza A rising from <1/2 to 1/64 and for Sendai rising from <1/4 to 1/16). This may be regarded as evidence of a dual infection, or, alternatively, it might be due to an anamnestic response of one of the antibodies. Influenza virus A and Sendai virus infection also occurred about the same time in the hospital for the chronic sick (Bruce White *et al.*, 1957).

From work proceeding at the moment, there appears to be an antigenic relationship between the virus of mumps and Sendai virus. A proportion of patients suffering from mumps, having the usual fourfold or greater rising antibody titre to mumps virus particle antigen, had, in addition, fourfold or greater rising titres to Sendai virus when the paired sera were examined by complement-fixation tests. A proportion of single sera sent to this laboratory having a high titre to mumps virus particle antigen also had a raised titre to Sendai antigen by complement-fixation tests. Until more information has been obtained on this point, all sera suspect of containing Sendai antibodies are being tested with mumps virus particle antigen.

Case 10 shows a fourfold rise to mumps virus particle antigen as well as to Sendai (the antibody titre for Sendai rising from <1/4 to 1/16 and that for mumps from <1/4 to 1/8). Shortage of serum prevented further investigation of this interesting case. The serological findings in this case are open to at least three interpretations. In the first place, it is possible that this was a case of mumps virus infection in which Sendai complement-fixing antibodies were evoked by an anamnestic reaction. Clinically this was unlikely, since the patient had none of the stigmata of mumps. In the second place, the infection may have been with Sendai virus, which provoked a mumps virus particle antibody response of the anamnestic type. A third possibility is that Sendai virus, or some strains of the virus, share an antigenic component with mumps virus, or some strain of mumps virus, with the result that infection with Sendai virus produces antibodies capable of reaction with both viruses in the complement-fixation test. The true explanation is at the moment doubtful, but it is of interest that Chanock (1956), in the U.S.A., found a relationship between his "croup agent" and mumps virus.

Where possible, patients were questioned for a past history of mumps, and this is recorded in the Table. It is worth noting that Case 14 had a definite history of mumps nine

months earlier. She was found to have a raised but unchanging titre of complement-fixing antibodies to mumps virus particle antigen in her two specimens of sera (the titres of Sendai complement-fixing antibodies showed a rise from 1/16 to 1/64, but the corresponding titres of mumps complement-fixing antibodies were 1/32 and 1/32).

In the 23 cases reported here evidence of Sendai infection was found in retrospect and no specimens of throat washings or swabs were available for isolation tests. The failure, so far, to isolate a virus only stresses the importance of obtaining suitable specimens for attempted virus isolation from cases of suspected influenza.

Summary and Conclusion

During 1956 the 872 suitably paired sera from cases of respiratory illness sent to this laboratory for investigation were examined for evidence of complement-fixing antibodies to Sendai virus.

Twenty-three cases of respiratory illness have been described in which a fourfold or greater rise in titre of complement-fixing antibodies to Sendai virus was found.

The illnesses varied from a mild influenza-like malady to a severe pneumonia; cough and laryngeal symptoms were often prominent. Cases were found in both sexes and among all age groups.

Evidence of an antigenic relationship between mumps and Sendai antigens was found. This was illustrated in a proportion of patients suffering from mumps who showed a rise in complement-fixing antibodies to both Sendai and mumps virus particle antigens.

Only one case in the present series gave a rising titre of complement-fixing antibodies to both Sendai and mumps virus particle antigen. The possible cause of this is discussed.

The C.F.T. for Sendai virus infection appears to be reliable, and a diagnosis can be readily made by serological means in cases of respiratory illness. Cross-reactions did not occur with other virus antigens used during the routine investigation of sera for respiratory illness.

Sendai virus or a related virus should be considered as a possible cause of respiratory disease, especially during the winter months.

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REFERENCES

- Chanock, R. M. (1956). *J. exp. Med.*, **104**, 555.
 Fukumi, H., Nishikawa, F., and Kitayama, T. (1954). *Jap. J. med. Sci. Biol.*, **7**, 345.
 Jensen, K. E., Minuse, E., and Ackermann, W. W. (1955). *J. Immunol.*, **75**, 71.
 Kuroya, M., Ishida, N., and Shiratori, T. (1953). *Yokohama med. Bull.*, **4**, 217.
 Sano, T., Niitsu, I., Nakagawa, I., and Ando, T. (1953). *Ibid.*, **4**, 199.
 White, G. B. B., Gardner, P. S., Hope-Simpson, R. E. (1957). *British Medical Journal*, **1**, 381.

NEWBORN PNEUMONITIS VIRUS (TYPE SENDAI)

EVIDENCE OF INFECTION IN SOUTH-WEST SCOTLAND

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The newborn pneumonitis virus (N.P.V.) (type Sendai) was isolated by Kuroya *et al.* (1953) from the lungs of newborn infants who died during an outbreak of pneumonitis in the wards of the department of paediatrics of the Tohoku University, Japan. The virus was cultured by intranasal inoculation of mice and was subsequently adapted to the allantoic cavity of the embryonated egg. Isolations of N.P.V. were reported about the same time by Misao (personal communication to Kuroya *et al.*) and Ohashi (personal communication to Kuroya *et al.*), from an epidemic of A prime influenza; later Matsuzawa *et al.* (1954) found antibody to the virus in healthy adults in various parts of Japan.

In the U.S.A. Jensen *et al.* (1955) found antibody to N.P.V. by haemagglutination inhibition tests in about 40% of paired sera from a variety of illnesses. These authors observed the highest levels of antibody in the under 18 age group, and in serum from more than 559 varied illnesses they found eight instances of what they considered a significant rise in antibody titre to N.P.V. In only two patients were they able to correlate rising titres of antibody with a clinical illness: one patient was diagnosed as a case of atypical pneumonia; the other case as a mild respiratory illness.

This paper presents evidence for the existence in south-west Scotland of an antigenic stimulus producing antibodies to N.P.V. Antibody was discovered on routine screening of paired serum specimens. Fourfold rising titres were observed in nine instances by complement-fixation tests; clinical details of these are summarized. No attempts were made to isolate the virus.

Methods

The population investigated and the techniques used have been described briefly in a previous paper (Grist, Somerville, and Carson, 1957). During the winter seasons of 1955 and 1956 the sera were drawn from three sources: paired sera were obtained from 175 adults admitted to the pneumonia wards of Ruchill Hospital, Glasgow; 97 pairs were obtained from infants admitted to the infant pneumonia wards of the same hospital; and 172 serum pairs were provided from cases of upper respiratory illness by general practitioners participating in the scheme for detection of influenza in the community during the course of influenza vaccine trials by the Medical Research Council (1955). In every instance the interval between collection of the serum samples in a pair was more than 7 and usually between 10 and 14 days.

The Sendai strain of N.P.V. was supplied by the World Influenza Centre of the World Health Organization. This virus was passed by the allantoic route in embryonated eggs at the eleventh day of incubation. Allantoic fluids were harvested and pooled 72 hours after incubation with 0.1 ml. of 1/1000 dilution of virus. After titration in "chess-board" experiments the pooled allantoic fluid was used at an