November 11, 1961

To Members of the Committee on Enteroviruses:

Dr. Gilbert Dalldorf
Dr. John F. Enders
Dr. Henry M. Gelfand
Dr. W. McD. Hammon

Dr. Robert J. Huebner
Dr. Leon Rosen
Dr. Albert E. Sabin
Dr. Herbert A. Wener

At the meeting of the Committee held on 6 November, the nomenclature report was discussed once again, and some changes were made in an attempt to make the report acceptable to all members of the Committee. A modified report, enclosed herewith, was unanimously adopted at the meeting, and the Chairman was instructed to submit the report for publication in Virology, which has now been done.

Sincerely yours,

Joseph L. Melnick

cc: Dr. Marvin Harris
    Dr. T. E. Boyd

To Drs. Dalldorf, Hammon, Sabin:

I am also sending a copy of our report to each member of the International Committee, of which you are members, in order that this group may be informed of this suggestion of the U. S. Committee, and in order to obtain their comments in preparation for the Nomenclature Committee meeting to be held in Montreal next summer.
Classification of Human Enteroviruses

The Committee on Enteroviruses deals with the classification of the already known poliomyelitis, Coxsackie, and ECHO viruses and with the establishment of newly discovered and characterized viruses as new prototypes. In the course of its work, the Committee has been confronted time and again with new strains which do not fit comfortably into one or another of the subgroups. Furthermore, as new strains of established types are discovered and studied, some turn out to have biological properties different from those of the prototypes, with the result that the same virus is considered an ECHO virus by some investigators and a Coxsackie virus by others. Thus ECHO 9 is sometimes referred to as Coxsackie A23 because strains are known which produce myositis and paralysis in mice. More recently, strains of Coxsackie virus (Type A21) and of ECHO virus (Type 28) have been reported as respiratory disease or common cold viruses deserving special classification in a new group of cold or rhinoviruses. Some strains, at least when first isolated, grow best in cell cultures under conditions different from those previously found optimal for the enteroviruses, and do not readily produce myositis in mice. These, however, are known to be highly variable characters, frequently representing only intratypic strain differences.

Because of the fuzzy boundary lines between the currently accepted subgroups of enteroviruses, and because certain strains seem to belong in one subgroup while other strains of the same immunologic type seem to belong to another subgroup, the Committee suggests that the presently known enteroviruses be classified in a simple numerical system on an antigenic basis and that each new antigenic prototype be assigned the next sequential enterovirus type number with no designation of a subgroup. This classification is recommended for use until adequate knowledge becomes available to permit establishment of properly defined subgroups.
**Definition.** Enteroviruses are transient inhabitants of the alimentary tract (although they may be found also in the nasopharynx). They exist in multiple antigenic types, with the following properties: (1) particle size about 28 nm in diameter, (2) ribonucleic acid core, (3) ether resistance, and (4) cationic stabilization to thermal inactivation. Some strains produce neural lesions in primates and rodents; others produce lesions in the muscle, pancreas, and brown fat of newborn mice; and others have not produced illness in any test animal. Most strains are cytopathogenic for primate cells, but several have not yet been cultivated in cell cultures. Although monkey kidney cell cultures are preferred for most enterovirus types, some strains are known which grow best or only in human embryo or amnion or in HeLa cell cultures. Some strains are more fastidious as to growth requirements than most, and grow optimally at 33-34°C under slightly acidic conditions in roller cultures. Some strains possess specific hemagglutinins; others do not. They contain complement-fixing antigens which are specific when used with hyperimmune sera prepared in laboratory animals.

The host range varies greatly from one type to the next, and even strains of the same type vary in this property. Enteroviruses may readily be induced, by laboratory manipulation, to yield variants which have host ranges and tissue tropisms different from those of certain wild strains; actually, this property has led to the purposeful development of attenuated vaccine strains.

Many of the enteroviruses cause diseases in man ranging from severe paralysis, to myocarditis, to skin rashes, to common colds, depending upon the target organ attacked. However, infection is usually at the subclinical level, with clinically manifest disease being more common for some types than for others. Different enteroviruses, as well as viruses outside the group, may
produce the same syndrome; on the other hand, the same enterovirus may cause more than a single syndrome. For these reasons, clinical disease has not been considered satisfactory as a basis for classification.

**New numbering system.** It is desirable to avoid future assigning of antigenically identical variants of the same virus to more than one subgroup, and to avoid shifting a virus from one subgroup to another as its strains become more fully characterized. Therefore the Committee now suggests a simple numerical system for classifying the enteroviruses by antigenic types. The table below lists the enteroviruses according to the new numbering system, together with their synonyms. Closely related serotypes are consolidated under a single enterovirus number. When a new prototype is discovered (as for example, Enterovirus 59), it will be assigned a new enterovirus type number with no further subgrouping.

It is suggested that for the next few years the new enterovirus numbers and the old names of the well known viruses be used parenthetically, e.g., Coxsackie B1 (Enterovirus 27). This would serve to avoid confusion and also to acquaint readers with the existence of a new nomenclature.
Data to be Submitted on New Human Enterovirus Candidates

REQUIRED DATA

1. Evidence of human origin. Demonstration of a significant neutralizing antibody rise in a person yielding the virus, or re-isolation of the agent from the original specimen and demonstration of antibodies in human sera or gamma globulin.

2. Lack of essential lipids (ether resistance). Demonstration of resistance to 20 per cent ethyl ether for 18 hours at 4°C (or to detergents).


4. Antigenic distinctness from all previously described human enterovirus serotypes. For the purposes of this requirement a virus is considered distinct if 20 units of antibody against the "broadest" available strain of other serotypes fail to neutralize 100 ID$_{50}$ of the candidate virus and vice versa. The candidate virus used in neutralisation tests and in preparing antisera must have been purified by the plaque or terminal dilution method. It must be shown that the virus which was used was not a mixture of two different agents.

RECOMMENDED DATA

1. Host range. Demonstration of a cytopathogenic effect in tissue cultures or pathologic effect in animals similar to that produced by one or more of the accepted serotypes.

2. Hemagglutinin. If candidate virus yields a positive hemagglutination test, cross HI tests should be carried out with other enterovirus serotypes known to possess this property.
3. Complement-fixing antigen. If possible, a CF antigen for the candidate virus should be tested against type-specific sera for each of the previously recognized serotypes.

4. Ribonucleic acid. If possible, the virus should be shown to contain ribonucleic acid (susceptibility of infective nucleic acid to RNA-ase and resistance to DNA-ase, red staining reaction with acridine orange, failure of 5-fluorodeoxyuridine to inhibit viral growth).

5. Cationic stabilization to thermal inactivation. Demonstration of full infectivity after heating virus at 50°C for one hour in presence of molar MgCl₂.

Committee on Enteroviruses*

Joseph L. Melnick (Chairman)
Gilbert Dalldorf
John F. Enders
Henry N. Gelfand
William McE. Hammon
Robert J. Huebner
Leon Rosen
Albert B. Sabin
Jerome T. Syvertson (deceased)
Herbert A. Wenner

* The Committee on the ECHO viruses was set up in 1955, sponsored by The National Foundation. In 1957, the membership was enlarged and the name changed to the Committee on Enteroviruses. Sponsorship was transferred to the National Cancer Institute, National Institutes of Health, in 1960.
## Human Enteroviruses: Type Numbers and Synonyms

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