FILTERABLE VIRUS DISEASES AND THE NATURE OF THEIR CAUSATIVE AGENTS

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Our modern study of this group of interesting diseases should be dated from 1886, when the Guarnieri bodies of small-pox lesions were first described. Eight years later the filtrability of the first virus (mosaic of tobacco) was demonstrated, and since that time attention has been given, and much information has been collected, concerning filterable viruses.

Recognizing the fact that obscurity still shrouds a large part of this study, and that as yet no hard and fast classification exists, we, nevertheless, in the interests of producing order and banishing chaos, have attempted to classify these viruses according to our evaluation and interpretation of experiment and perusal of contemporary literature.

CLASSIFICATION OF VIRUS DISEASES

I. Virus Diseases with Cell Inclusions which are Definitely Proved Transmissible and Filtrability of the Causative Agent is Established.

A. Diseases of Man:

1. **Small-pox**
   Varioloid.
   Vaccinia.
   Paravaccinia.
   Alastrim.
2. **Verruca (common warts).**
3. **Molluscum contagiosum.**
4. **Rabies.**
5. **Herpes febrilis.**
6. **Papilloma of the larynx.**
7. **Yellow fever.**

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B. Diseases of Lower Animals:
  1. Pox diseases
    Cowpox.
    Sheep-pox.
  2. Virus III infection of rabbits.
  3. Borna disease.
  4. Distemper.
  5. Foot-and-mouth disease.
  6. Myxomatosis of rabbits.
  7. Rabies.
  8. Hog cholera.
  9. Infectious pustular stomatitis of horses.
  10. Salivary gland disease of guinea pigs.
  11. Rift Valley fever (enzoötic hepatitis).
  12. Louping-ill.

C. Diseases of Fowls:
  1. Fowl pox (avian diphtheria).
  2. Fowl plague.
  3. Virus disease of parrots and parrakeets.
  4. Fowl laryngotracheitis.

D. Diseases of Insects:
  1. Polyhedral diseases
    Gipsy-moth caterpillar.
    European moth caterpillar.
    Tent caterpillar.
    Jaundice of silkworms.

E. Diseases of Plants:
  1. Mosaic diseases
    Common examples.
      Tobacco, Tomato, Potato.

II. Virus Diseases with Cell Inclusions which are Transmissible but Filtrability of the Causative Agent has not been Established.

A. Diseases of Man:
  1. Varicella.
  2. Inclusion Blennorrhoea.

B. Diseases of Lower Animals:
  1. Horse-pox.

C. Diseases of Insects:
  1. Polyhedral disease of the black arches moth caterpillar.

D. Diseases of Fish:
  1. Lymphocystic disease.

III. Virus Diseases with Cell Inclusions which are not Transmissible and Filtrability of the Causative Agent has not been Established.

A. Diseases of Man:
1. Herpes zoster.

B. Diseases of Fish:
1. Carp-pox.
2. Epithelioma of Barbus.

IV. Virus Diseases with no Cell Inclusions which are Transmissible and the Filtrability of the Causative Agent has been Definitely Established.

A. Diseases of Man:
1. Epidemic parotitis.
2. Foot-and-mouth disease.
3. Pappataci fever.
4. Poliomyelitis.
5. Dengue fever.
6. Psittacosis.
7. Common colds.

B. Diseases of Lower Animals:
1. Nairobi disease of sheep.
2. Catarrhal fever of sheep.
3. Equine influenza.
4. Vesicular stomatitis in horses.
5. Rinderpest (cattle plague).
6. Ephemeral fever in horses and cattle.
7. Epizoötic in guinea pigs.
8. Guinea pig paralysis.
9. Novy's rat disease.
10. Cattle warts.
11. Fox encephalitis.
12. Noguchi's (*Dermacentor andersoni*) virus infection in guinea pigs and monkeys.
13. Pseudorabies (infectious bulbar paralysis) (Mad Itch).
14. Pleuropneumonia in cattle.
15. Agalactia of sheep.
16. Anemia of rats.
17. Equine infectious anemia.
18. African horse sickness.
19. Swine influenza.

C. Diseases of Fowls:
1. Rous' chicken sarcoma.
2. Philippine fowl disease (Newcastle or
3. Leukemia of chickens.

D. Diseases of Insects:
1. Sacbrood disease of bees.

V. A Group of Diseases in some cases of which Claims have been made for Specific (Bacterial, Protozoal, Rickettsial, etc.) Etiological Agents, in many of which the Filterable Nature of the Causative Agent Remains Questionable but Suggestive: And in Others Inclusion Bodies have been Reported and their Identification is either Established or Remains Doubtful.

A. Diseases of Man:
  1. Scarlet fever.
  2. Trachoma.
  3. Encephalitis
     Epidemic encephalitis.
     Vaccinial encephalitis.
     Australian X disease.
     Encephalitis following measles.
     Encephalitis following mumps.
     Encephalitis following varicella.
  4. Epidemic influenza.
  5. Measles.
  6. German measles.
  7. Multiple sclerosis.
  8. Tsutsugamushi disease.
  9. Psoriasis.
  10. Condyloma acuminatum.
  11. Visceral disease.

B. Diseases of Lower Animals:
  1. Puppy disease.
  2. Swine pox.
  3. Goat pox.
  4. Kurloff bodies in guinea pigs.

C. Diseases of Fowls:
  1. Fowl paralysis (Neurolymphomatosis).
  2. Macfie's disease of fowls.

D. Diseases of Insects:
  1. Grasserie of the caterpillar of the large white cabbage butterfly.
  2. Nuclear disease of the caterpillar of the large white cabbage butterfly.

E. Diseases of Amphibia:
  1. Todd bodies.

Regarding the nature of ultramicroscopic viruses, the actual size of any of them remains undetermined, and even after the most minute examination we have only a relative idea of their probable dimensions, and no knowledge as to whether particles of these infinitisimal agents have independent existence. For example: the bacteriophage is said to measure from 20 to 200 millimicrons; fifty molecules of crystaline egg albumin are thought to measure from 4 to 10 millimicrons in diameter; such viruses as the Rous sarcoma and herpes appear to be smaller than this. It would seem that the ultramicroscopic viruses are, in general, about the size of secondary colloidal particles (5 to 100 millimicrons) and some may possibly be as small as primary colloidal particles (2 to 20 millimicrons), or even as small as the molecule (0.2 to 5 millimicrons), which is regarded hypothetically as the simplest form of life.

Equally indefinite are the reports dealing with electrical charge of the various viruses. The main obstacle to accuracy in this respect is the impossibility of separating viruses from associated proteins which may themselves determine the electrical charge, and may mask that of the viruses themselves. It is known that such viruses as vaccinia and fowl-pox are adsorbed by india ink, kaolin, baked kielselguhr and charcoal. The Rous sarcoma virus, however, is not adsorbed by these substances, but is inactivated by such a substance as carmine in certain concentrations. Here again, however, we do not know if the apparent affinities of these substances for the viruses in question exist for the viruses themselves or for the proteins upon which these agents are adsorbed, or for both.

One of the characteristic properties of viruses is their resistance to certain physical and chemical agents. For example, the resistance of several viruses to glycerol is well known. On the other hand their susceptibility to salt solutions is also well recognized. Virus-in-tissue stored in glycerol is known to be quite susceptible to subsequent autolytic processes which occur in the tissue framework. While viruses in general seem to have a somewhat greater resistance to higher temperatures than bacteria, we have seen no study involving several viruses in which temperature and time of exposure have been controlled for each agent, and in which careful titration of virulence has been determined in connection with such investigations.

Viruses exhibit certain tendencies to attack definite cells, and their effect may be stimulating or destructive in character. Many are associated with the production of inclusion or intracytoplastic bodies in the cells attacked, but whether they actually provoke the formation of bodies is as yet unknown. We have already indicated that viruses seem to possess affinities for certain types of cells; that these apparent tropisms may be altered to some extent is well established. With altered tropism in a given virus there may also be an altered manifestation of virulence of the virus and in such cases it would seem evident that a fundamental biological change may be brought about in certain virus strains. The viruses of vaccinia and of yellow fever are excellent examples of such changes brought about by passage in different animal hosts.

Though the nature of the inclusion body is uncertain, we know that it contains, or is largely composed of, virus, as in the cases of fowl-pox. Recent studies on the microincineration of virus-infected tissue in which inclusion bodies are found, such as rabies-infected tissue and yellow fever tissue, have thrown some new light on the character of these particular inclusion bodies. It has been found, for example, that the ash remaining after microincineration is quite different, in the case of acidophilic nucleoli, from that of inclusion-laden nuclei, but this will no doubt be discussed in greater detail in another paper during this symposium.

One of the most important phases of the virus problem is that of the actual cultivation of these agents, rendered very difficult by the fact that no virus has, as yet, been cultivated outside a susceptible host in any medium which does not contain living cells. In future work with these agents, artificial cultivation is the as yet unattainable goal. However, in our recent work, though we have not been able to demonstrate actual multiplication of such viruses as pigeon-pox, herpes and myxoma on artificial mediums, under varying gaseous tensions we have learned something regarding mere survival or viability under these conditions. Employing gaseous tensions of 50 per cent helium, 40 per cent oxygen and 10 per cent carbon dioxide and different temperatures ranging from 5°C to 37.5°C it appears that the viruses such as herpes and pigeon-pox may easily be maintained in virulence on artificial mediums for many weeks in temperatures ranging as high as 20°C, but they do not survive at higher temperatures. The virus of myxomatosis of rabbits is apparently very susceptible to the physical conditions imposed under such gaseous tensions and does not survive beyond the first week, showing a difference between this virus and the two former ones. These results cannot be considered of great value as actual multiplication was not demonstrated.

The desirability of considering the filterable viruses as a special group of disease-producing agents, is again emphasized. Recently an attempt has been made to intrude socalled filterable microbes and bacteria into the virus group, and indict them as etiological agents in such diseases or conditions as epidemic encephalitis, poliomyelitis, herpes zoster, spasmodic torticollis, epidemic hiccup, ulcerative colitis, gastric ulcer, arthritis deformans, rheumatism and rheumatic fever, epidemic influenza, infectious arrhythmia, chorea, measles, german measles, pulmonary embolism, post-operative hiccup, etc. A selected few of these diseases we still include, with good reason, among the filterable virus group. We may properly question if some of these conditions are disease entities at all—and suggest that some may be merely symptoms of more complex syndromes.

Most authorities still feel that with the filterable viruses we are most probably dealing with a special group of agents differing from such forms as bacteria. The tendency of virus infections to establish a lasting immunity to subsequent infections, the fact that only living virus will produce immunity artificially, the marked tendency of viruses to attack tissue cells from within with the formation in many cases, of intracellular inclusion bodies; all serve to differentiate viruses from bacteria. Besides these fundamental differences we may add that viruses are not cultivable on artificial mediums as are most bacterial forms.

Etiologically, histologically, immunologically and epidemiologically more evidence is accumulating to substantiate this fundamental concept.