Bull. Org. mond. Santé
Bull. World Hlth Org. } 1953, **8**, 755-774

THE INFLUENZA PROGRAMME OF WHO *

A. M.-M. PAYNE, M.D., M.R.C.P.

Division of Communicable Disease Services, World Health Organization

SYNOPSIS

This article describes the evolution of international co-operation for the control of epidemic influenza, from the founding of the United States Armed Forces Commission on Influenza in 1941 to the present network of influenza centres designated by WHO in 42 different countries. The technical problems of dealing with this disease on a worldwide scale are indicated, and their bearing on the development of the WHO influenza programme discussed. Suggestions are made for the simplification and co-ordination of the system on which epidemiological information is compiled, and the need for speed in both its collection and its dissemination is emphasized.

Influenza recognizes no man-made boundaries; indeed, many of the achievements of man increase the speed and extent of its spread. The appearance of epidemic influenza is viewed with concern in the country initially involved, among neighbouring nations, and indeed in all continents. It was natural, therefore, that the nations of the world should call on their own intergovernmental Health Organization to play a co-ordinating role in the struggle against the disease.

It may be useful first to examine briefly the reasons for concern at the appearance of epidemic influenza, since it will help to define the objectives of a worldwide plan.

The first reason is the memory of the 1918-19 pandemic. Many readers will recall the appalling suddenness with which it killed healthy young people, the speed with which it spread, and the futility of all efforts to control it. It paralysed whole cities, even whole countries; food distribution broke down, and the economic loss was enormous. It killed more than 15 million people. No one knows whether this disaster will ever occur again, for no one knows the combination of circumstances which brought it about. However, assuming that it was caused by a variant of the influenza virus, there is a real basis for anxiety because, within certain limits, the virus shows no stability in nature and, as far as is known, a variation that has occurred once may occur again.

* This article will also be published, in Spanish, in the *Boletín de la Oficina Sanitaria Panamericana.*

The second cause of concern is the highly infectious nature of the disease and the fact that it appears to produce no permanent immunity. When influenza is epidemic one tends to think—not, whether one will get it, but when will one get it ? Allied to this is its short incubation period and the speed with which it spreads. If smallpox broke out 500 miles away, for example, one would not feel anxious, but with influenza one would quite rightly fear that it might arrive within a short period.

The third reason is the effect of influenza on the economics of a country. This is naturally very difficult to measure; however, we have only to look at records such as national insurance claims or records of absenteeism in factories to realize that it may be considerable.

Finally, but not least, influenza or its main complication, pneumonia, does kill. In Liverpool, for example, in 1951 the weekly death-rate exceeded the highest figures of the 1918 pandemic, although this time it was mainly the old who died; in the Netherlands in 1949, 2,200 people died within a short period.

This, then, is the objective of the WHO influenza programme : first, to plan against the possible recurrence of a pandemic; second, to devise control methods to limit the spread and severity of the disease; and lastly, to limit the economic effects of an epidemic. Which of the three is regarded as the most important depends on the point of view. However, in the light of present knowledge they can all only be approached in one way.

Before showing how this is being attempted, it is necessary to touch briefly on some technical questions which are really the roots of the whole problem. These are considered in much more detail in the articles by Dr. C. H. Andrewes and Dr. T. Francis, jr.[a] Nevertheless, a summary here will help to explain the way in which the WHO programme was developed.

Three main types of the virus of influenza have so far been discovered; the two most important of them—A and B—comprise several subgroups. In the case of virus A these may differ so much as to afford little or no protection, after infection or vaccination, from subsequent infection by a virus of a different subgroup.

This was demonstrated in 1947 (Francis et al. [4]) when a vaccine made from a strain of virus A (PR8) which had given good results in the 1943-4 outbreak,[7] failed to give any protection at all. It turned out that the virus causing the 1947 epidemic was of another subgroup (FM1) now often referred to as A-prime (Salk & Suriano [6]) which differs considerably from PR8. This subgroup of virus A was first detected in Australia in 1946 (Cam). In retrospect that was a most important observation, because if we had known then what we know now there would have been time to prepare a vaccine before the 1947 outbreak. Nevertheless, the danger

[a] See pages 595 and 725.

of the sudden appearance of a new strain of virus remains one of the most serious problems.

Apart from the antigenic variation just described, strains of virus may differ considerably in their ability to spread and to kill. For example, in 1951 the so-called " Liverpool " strain of A-prime virus caused a lethal outbreak in that town, whereas the so-called " Scandinavian " strain spread widely but caused only mild influenza (Isaacs et al.[5]). Yet these strains were so similar antigenically that they were only distinguished by the use of ferret antisera. The strains differed also in their power to stimulate antibody production. The latter quality is obviously highly important in selecting strains for incorporation in vaccines.

The third technical point is that during an epidemic the virus breeds true, within certain limits; that is to say, an outbreak caused by one strain of virus A is not related to one caused by a different strain, even if it occurs nearby and at about the same time. For example, in this year's (1953) epidemic the virus responsible for influenza in southern England was sufficiently different from that found in northern France to make it clear that there was no relation between the two outbreaks, even though the Channel is a trivial obstacle to the influenza virus. On the other hand the virus responsible for the epidemic in the United States of America was similar to the British virus. However, this does not justify the conclusion that the outbreaks were related, because a closely related strain had previously been detected in both countries in 1951 and may have remained there ever since. How the virus maintains itself in the intervals between epidemics is not yet known.

The consequences of these facts are :

(1) that successful vaccination against influenza depends on knowledge of the virus causing the epidemic;

(2) that continuous vigilance is necessary to detect new and potentially dangerous strains of virus at the earliest possible moment; and

(3) that epidemiological reports can be correctly interpreted only in terms of laboratory studies of the viruses responsible.

These are the technical conclusions which must be considered in planning to attain the objectives already set out. It will be seen that the essential knowledge required is early information regarding the nature of the virus causing an outbreak, and a careful analysis of its characters, especially its antigenic structure; and that this information must be gathered from as wide a geographical area as possible. This was appreciated as long ago as 1941, when the US Armed Forces Commission on Influenza, under the chairmanship of Dr. T. Francis, jr., set up a network of laboratories for the isolation of influenza virus, with a central reference laboratory known as the Strain Study Center under Dr. T. P. Magill; its function, as the name implies, was to study and compare strains of virus isolated

in different places. Valuable though the work done by this organization was, its usefulness was inevitably restricted by national boundaries.

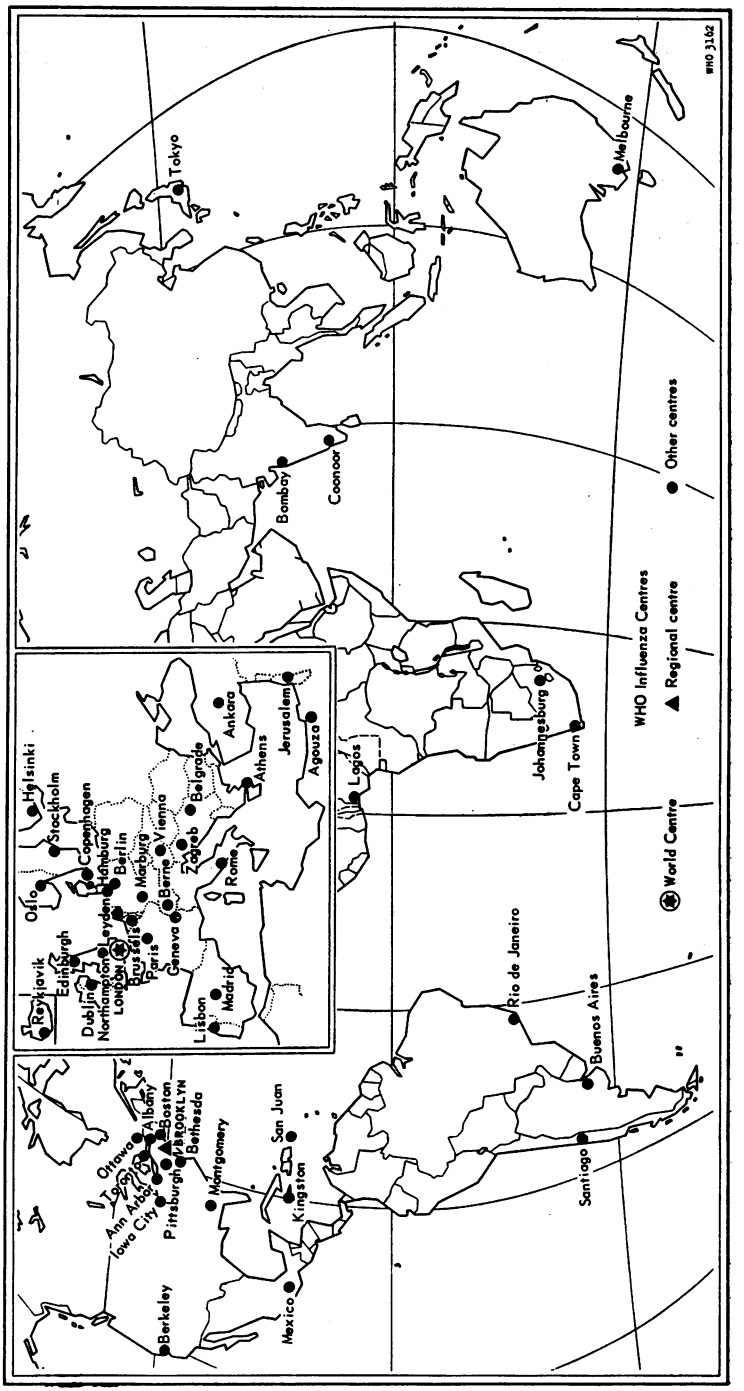
On 3 April 1947 at its third session the attention of the Interim Commission of the World Health Organization was drawn to the problems and dangers of epidemic influenza by a proposal of the Representative from the Netherlands that a small committee should be appointed to consider the problems.[8] After discussion, the Commission instructed the Executive Secretary to send an observer to the Fourth International Congress on Microbiology, to be held in Copenhagen in July of that year, to obtain from the experts gathered there as complete information as possible on the subject. At Copenhagen an informal meeting of 45 interested people was held at the Rigsdag on 25 July, and after discussion a small committee of nine members from nine countries was chosen to consider how the views expressed could best be put into practice. At the committee's request Dr. C. H. Andrewes (United Kingdom) prepared a memorandum embodying the suggestions made, which was placed before the Interim Commission at its fourth session in September 1947.[9]

The proposals were that a World Influenza Centre (WIC) should be set up with responsibility for collecting and distributing information, carrying out and co-ordinating laboratory work on influenza, and training laboratory workers. It would work in close co-operation with a number of regional laboratories. The Interim Commission [9] accepted the proposals and decided to establish and finance an international influenza centre in England, and to ask Dr. Andrewes to begin the work as recommended in his memorandum. The Medical Research Council of Great Britain agreed to the establishment of the WIC at the National Institute for Medical Research in London, and the WHO influenza programme had begun.

Work commenced at once, but the organization of a worldwide network of laboratories takes time, and indeed is not completed yet, since in a number of countries there are no virus laboratories and no trained virologists. During the winter of 1947-8 the USA was invited and agreed to participate in the co-operative programme (Culbertson; [2] see also Davis [3]). The Strain Study Center under Dr. Magill, already mentioned, was designated the National Strain Study Center for the United States of America, and the programme was largely built around it, utilizing the existing facilities for investigating influenza, especially those under the Armed Forces Commission on Influenza. An Influenza Information Center was established at the National Institutes of Health, Bethesda, Md., to administer the programme under a committee designated by the Surgeons-General of the Army, Navy, Public-Health Service, and Air Force, and to act as the liaison office between the WIC in London and the co-operating laboratories in the USA.

As the network developed it became clear that there would be great advantages both in speed and in convenience if a single reference laboratory

FIG. 1. WHO INFLUENZA CENTRES



served the whole of the American region. Accordingly the US Strain Study Center accepted designation as the Strain Study Center for the Americas, and now acts for the whole continent exactly as the Centre in London acts for the rest of the world. The two reference laboratories co-operate closely so that the overall world picture can be seen.

There is now a total of 54 WHO-designated influenza centres in 42 countries, but of these 27 are in Europe and 11 in North America. In Central and South America there are 6, in the Eastern Mediterranean Region there are 2, in the African Region 3, in South-East Asia 2, and in the Western Pacific 3. A complete list of centres will be found in Annex 1 (page 765) (see also fig. 1).

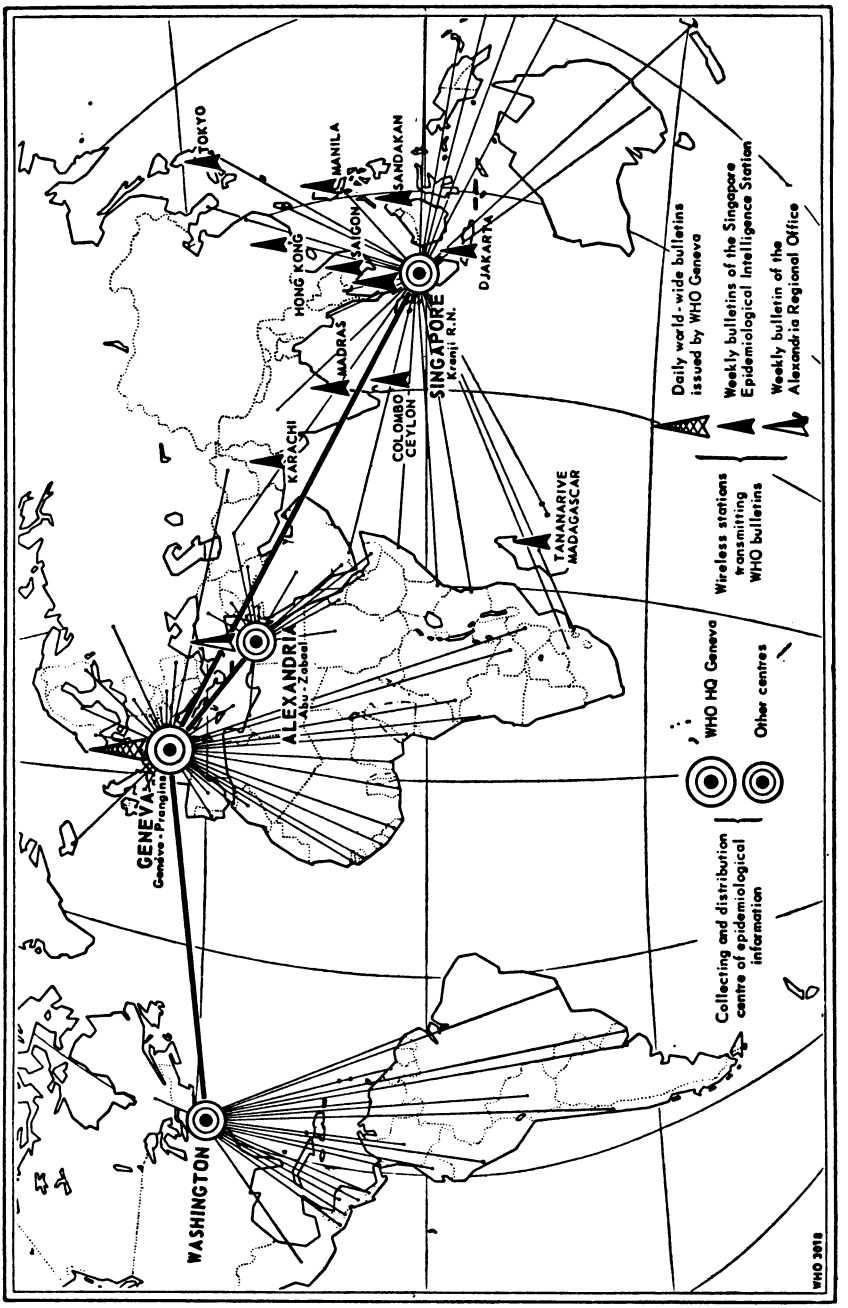
There are other laboratories co-operating informally in various regions, especially in the USA, but it is clear that the network is not yet worldwide. Efforts are being made to extend the coverage with the help of the WHO regional offices (see Annex 3, page 772). As a temporary solution a number of Influenza Observers (see Annex 2, page 771) have been designated. They are unable to undertake laboratory studies but they furnish epidemiological reports.

The functions of an Influenza Centre are twofold :

First, to report with all speed the occurrence of influenza within a country, with an estimate of its extent and severity. This information is sent in parallel to the Epidemiological Information and Morbidity Statistics Section at WHO Headquarters in Geneva, to the appropriate regional office, and to the appropriate reference laboratory in London or New York. In the American Region the arrangement is slightly different. The reports from the USA and Canada are first collected by the national Influenza Information Centers which then transmit the information in the same way.

The collection of epidemiological information regarding influenza presents many difficulties. It is well known that notifications are relatively meaningless, because the clinical diagnosis of influenza has no scientific accuracy, and also, during an epidemic the more overworked a practitioner is the less time he has for notifying his cases. In addition, the speed with which influenza spreads makes a delay of only a few days in collecting and distributing the information highly important. What is needed is not a record of actual numbers of cases but some kind of index of the presence of influenza-like disease, based for example on absenteeism among public-transport workers, in factories, or in schools. If such information were collected regularly in selected towns, " normal " figures could soon be established, the simplicity of the information would greatly accelerate the speed of collection, and it might prove possible to follow the trend of an epidemic without the present time-lag. In time of epidemics information regarding the incidence of influenza is collected telegraphically from national health administrations. Frequently, however, the first news of an outbreak reaches the WHO Epidemiological Services from an Influenza Centre

FIG. 2. NETWORK OF EPIDEMIOLOGICAL RADIO-TELEGRAPHIC COMMUNICATIONS



and is followed by reports of laboratory results. The information is distributed in the several epidemiological weeklies issued and airmailed from Geneva, Alexandria, Singapore, and Washington, and—if sufficiently important—by cable and in the daily epidemiological radio bulletins (see fig. 2). In addition, summaries are sent by airmail to all Influenza Centres at regular intervals so that the information regarding the prevalent virus which is needed for the proper use of vaccines is available as soon as possible. Of course, if the pandemic recurred much greater use would be made of radio and cabled information.

The second function of an Influenza Centre is to identify the type of influenza by serological tests and preferably by virus isolation. The results are reported in the same way, and the viruses isolated are dried, frozen, and dispatched by air to the appropriate reference laboratory as soon as possible for further study and comparison with strains isolated elsewhere.

The latter function raises difficulties other than the mere mechanical ones of transport. When an unusual strain is isolated, it is natural to wish to characterize it fully before passing it on to others. This takes time and it is just these unusual strains which are potentially so important. They may be needed at once for the manufacture of vaccine because they may have unusual virulence and ability to spread. It is essential for the WHO programme that these strains should be made freely available the moment any unusual characters are recognized. The sense of international responsibility shown by the workers co-operating in this programme has been truly remarkable.

Strains showing obviously unusual characteristics, collected by the two reference laboratories, are exchanged without further delay, so that they are available for vaccine production in both hemispheres if necessary; they are also sent to other Influenza Centres on request. Most strains, however, do not show such unusual features and they are subjected to careful antigenic analysis and characterization by the reference laboratories to clarify their relationship with other strains. In order to avoid changes in the virus which may occur as the result of passage in the laboratory, early egg-passage material should be sent to the reference centres. As the epidemic proceeds, the epidemiological and virological evidence accumulates and when it is complete the epidemiological data are interpreted in terms of the laboratory results.

It has already been mentioned that it is not known how the influenza virus maintains itself between epidemics, nor is it fully understood how epidemics are generated. Sometimes good evidence of geographical spread of the virus is found, sometimes the disease suddenly appears simultaneously all over a large area as if a preliminary seeding of the virus had taken place throughout the population. The relative importance of the two methods seems to vary in different areas but it is easy to see the practical significance: if the spread is predominantly geographical (as appears to have been the

case in the 1948-9 A outbreak in Europe, which began in Sardinia and spread through Sicily, Italy, and thence through western Europe) (Chu et al. [1]) there may be time to vaccinate key-persons before the epidemic wave arrives. If, on the other hand, the virus seeds itself almost invisibly and then the epidemic breaks out everywhere at once, it is really too late to do anything which will have much effect. It is therefore highly important to understand more about the genesis of epidemics, since the future application of control measures will to a large extent depend on it. This investigation is one of the main functions of the two reference laboratories and obviously the study can only be made with international co-operation. Actually a good deal of progress is being made and this is reviewed in the article on the epidemiology of influenza by Dr. C. H. Andrewes.[b]

In co-ordinating the work of a large number of laboratories in many different countries, it is found that technical procedures vary in different places and sometimes the results obtained are not comparable. The experience of workers varies too, and many virologists ask for advice and guidance on new techniques. It is also important that new knowledge should be disseminated as widely and as quickly as possible, so that its practical application is not delayed. Sometimes special problems arise which need co-ordinated research for their solution. Sometimes several workers, unknown to each other, work for long periods on the same approach to the same problem, causing unnecessary duplication and waste of effort.

To overcome these difficulties WHO has evolved a system of Expert Advisory Panels and Expert Committees. Leading workers in a great variety of fields are invited to serve on these Panels, and undertake to advise on technical matters concerned with their own speciality and to keep WHO informed of important advances. From time to time, as determined by the World Health Assembly, Expert Committees, consisting generally of from six to ten members, are convened to report and advise on specific problems. The reports of the committees, after approval by the Executive Board of WHO, are usually published in the *Technical Report Series.*

An Expert Advisory Panel on Virus Diseases has been established to advise on influenza and other virus diseases, and an Expert Committee on Influenza [c] was convened in 1952. The committee reviewed the work of the WHO programme and made suggestions for more effective international collaboration. It studied certain technical questions, including the methods of comparing and typing strains, and diagnostic procedures, and gave precise details of recommended methods for performing diagnostic complement-fixation and haemagglutination-inhibition tests. It also

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[b] See page 595.

[c] The report of this committee has been published as *World Hlth Org. techn. Rep. Ser.* 1953, **64.**

described the preparation of antisera for the comparison and typing of strains of influenza virus, and the preparation and use of crude cholera filtrate for the destruction of inhibitors. Other subjects briefly reviewed included influenza virus vaccines, the collection and distribution of epidemiological information, control measures, and the therapy of influenzal pneumonia.

The recommendations of the Expert Committee should go a long way towards ensuring comparable results in different laboratories, and this will be aided by the proposed provision by WHO of standard diagnostic reagents to laboratories in the WHO network. A freer exchange of new knowledge can also be hoped for, as well as improved facilities for training workers in the techniques of virology.

It should, perhaps, be emphasized that although the WHO influenza network of laboratories was primarily organized for the study of influenza, very many, if not all, of the laboratories undertake a great deal of work on other virus diseases. The network is therefore potentially able to embark on a co-operative international study of other virus diseases, should such a need arise, and, with that in mind, it is regarded as important that training should cover virology in general and not be confined solely to the techniques used in the study of influenza.

Finally, what has the WHO influenza programme achieved so far, and what of the future ? Space does not permit a full account. Indications as to some of the results have already been given; others are reviewed by Dr. Andrewes, and details can be found in various publications, notably the *Bulletin of the World Health Organization*, to which references will be found in his paper.[d]

Possibly the most important achievement is that workers in 42 different countries are working in harmony towards a single end, with no financial reward and sometimes with a partial sacrifice of individual credit for the work. As a result, our knowledge of influenza virus variation and the epidemiology of influenza has increased enormously. The type of virus responsible for an outbreak is now usually known early enough for the information to be of practical value to countries not yet affected. For example, this year it was possible to inform the governments of certain countries which vaccine was the correct one to use before any influenza had broken out there. The choice of strains of virus for inclusion in vaccines clearly requires international consultation. This year, too, when telegraphic news was received of the Japanese epidemic, an unusual virus isolated in Japan in 1951 was at once dispatched by airmail to both Australia and the USA, in case it was responsible, and in time for a limited production of vaccine, had it been necessary. The virus was not responsible, but the mechanism is there and is working satisfactorily.

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[d] See page 595.

There are still many unsolved problems in influenza which are thoroughly reviewed by other contributors to this symposium and which need not be repeated here. There is hope that some of them will be solved in the near future, as a result of the extensive research now in progress in many parts of the world.

The WHO influenza programme is now a going concern and will continue to grow and improve in efficiency. It is there to apply on an international scale the new knowledge gained by national research, and to supplement that knowledge by international collaboration. Whether influenza will ever be controlled no one can tell, but the time when it will be possible to limit the effects of epidemic influenza to a significant degree appears to be within sight, and the WHO programme is helping to bring that day nearer.

Annex 1

WHO INFLUENZA CENTRES

International

World Influenza Centre
Dr. C. H. Andrewes
National Institute for Medical Research
The Ridgeway, Mill Hill
London, N.W.7

Strain Study Center for the Americas
Dr. T. P. Magill
State University Medical Center
New York College of Medicine
335 Henry Street
Brooklyn 2, N.Y.

African Region

NIGERIA
Virus Research Institute
Yaba
Lagos

UNION OF SOUTH AFRICA
Dr. J. H. S. Gear
The South African Institute for Medical Research
Johannesburg
in collaboration with
Professor M. van den Ende
Department of Pathology
University of Cape Town
Cape Town

American Region

ARGENTINA

Dr. A. S. Parodi
Section of Virus Epidemiology and Immunity
Instituto Bacteriologico Carlos G. Malbran
Avenida Velez Sarsfield 563
Buenos Aires

BRAZIL

Dr. J. G. Lacorte
Chefe de Seccao de Virus
Instituto Oswaldo Cruz
Caixa postal 926
Rio de Janeiro

CANADA

Dr. F. P. Nagler
Canadian Influenza Information Centre
Laboratory of Hygiene
Department of National Health and Welfare
45, Spencer Street
Ottawa

Dr. C. E. van Rooyen
The Connaught Medical Research Laboratories
University of Toronto
Toronto

CHILE

Dr. Raul Palacios
Virus Section
Instituto Bacteriológico de Chile
Santiago

JAMAICA

Dr. L. Grant
Department of Pathology
University College of the West Indies
Mona, St. Andrew

MEXICO

Dr. Gerardo Varela
Instituto de Salubridad y Enfermedades Tropicales
Esq. Carpio y Plan de San Luis
Mexico City 17

PUERTO RICO

Dr. J. E. Pérez
School of Tropical Medicine
University of Puerto Rico School of Medicine
San Juan 22

UNITED STATES OF AMERICA

Dr. Dorland J. Davis
Influenza Information Center
National Institutes of Health
Federal Security Agency
Bethesda 14, Md.

American Region *(continued)*

UNITED STATES OF AMERICA *(continued)*

Dr. M. F. Schaeffer
Communicable Disease Center
US Public Health Service
Montgomery, Ala.

Dr. E. H. Lennette
Division of Laboratories
California State Department of Public Health
1392 University Avenue
Berkeley, Calif.

Dr. A. P. McKee
State University of Iowa
Iowa City, Ia.

Dr. M. Finland
Boston City Hospital
Thorndike Memorial Laboratory
Boston, Mass.

Dr. T. Francis, jr.
Department of Epidemiology
University of Michigan School of Hygiene and Public Health
Ann Arbor, Mich.

Dr. I. J. Gordon
Division of Laboratories and Research
New York State Department of Health
Albany, N.Y.

Dr. J. E. Salk
University of Pittsburgh School of Medicine
Pittsburgh, Pa.

Eastern Mediterranean Region

EGYPT

Dr. Mohamed Aly & Dr. I. M. Hassan
Serum and Vaccine Laboratory
Agouza (Guizeh)

ISRAEL

Dr. H. Bernkopf
Hadassah Medical School
The Hebrew University
Jerusalem

European Region

AUSTRIA

Dr. E. Petrowsky
Bundesstaatliche bakteriologisch-serologische Untersuchungsanstalt
Währingerstr. 25a
Vienna 9

European Region *(continued)*

BELGIUM

Dr. P. Nélis
Laboratoire Central d'Hygiène
2 Parc du Cinquantenaire
Brussels

DENMARK

Dr. J. Ørskov & Dr. P. von Magnus
Statens Seruminstitut
80 Amager Boulevard
Copenhagen

FINLAND

Dr. Kari J. Penttinen
Valtion Serumlaitos
Fabianinkatu 24
Helsinki

FRANCE

Professeur R. Dujarric de la Rivière, Professeur Pierre Lépine, & Mlle G. Cateigne
Institut Pasteur
28, rue du Docteur Roux
Paris 15e

GERMANY (WEST)

Professor K. Herzberg
Hygienisches Institut der Universität Marburg
Marburg an der Lahn

Professor E. G. Nauck
Bernhard-Nocht-Institut für Schiffs- und Tropenkrankheiten
Bernhard-Nocht-Strasse 74
Hamburg 4

(BERLIN—WEST)

Professor D. Henneberg
Robert Koch Institut für Hygiene und Infektionskrankheite
Föhrerstrasse 2
Berlin N 65

GREECE

Dr. S. G. Pavlidis
Ministry of Hygiene
Central Public Health Laboratory
37, 28th October Street
Athens

ICELAND

Dr. B. Sigurdsson
University of Iceland Institute for Experimental Pathology
Keldur
Reykjavik

IRELAND

Dr. P. N. Meenan
St. Vincent's Hospital
St. Stephen's Green
Dublin C.2

European Region *(continued)*

ITALY

Professor I. Archetti
Istituto Superiore di Sanità
Viale Regina Margherita 299
Rome

NETHERLANDS

Professor J. D. Verlinde
Instituut voor Praeventieve Geneeskunde
Wassenaarscheweg 56
Leyden

in collaboration with

Professor J. Mulder
Interne Universiteitskliniek
Leyden

NORWAY

Professor Th. Thjøtta
K. W. Wilhelmsen og frues Bakteriologiske institutt
Rikshospitalet
Oslo

PORTUGAL

Dr. A. A. C. Sampaio
Dr. Ricardo Jorge Laboratorio de Bacteriologia Sanitaria do Instituto Superior de Higiene
Campo dos Mártires de Pátria, 91
Lisbon

SPAIN

Dr. F. Pérez Gallardo
Escuela Nacional de Sanidad
Facultad de Medicina
Pabellon No. 1
Ciudad Universitaria
Madrid

SWEDEN

Dr. A. Svedmyr
Statens bakteriologiska laboratorium
Box 764
Stockholm 1

SWITZERLAND

Professor E. Grasset
Institut d'Hygiène
Université de Genève
Geneva

Professor C. Hallauer
Institut für Hygiene und Bakteriologie
Berne

TURKEY

Dr. Niyazi Erzin
Refik Saydam Central Institute of Hygiene
Ankara

European Region *(continued)*

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

Dr. L. Hoyle
Public Health Laboratory
General Hospital
Northampton

Dr. R. H. A. Swain
Bacteriology Department
University New Buildings
Teviot Place
Edinburgh 1

Dr. F. O. MacCallum
Central Public Health Laboratory
Colindale Avenue
London, N.W.9

YUGOSLAVIA

Dr. A. Terzin
Bakteriološko Odelenje
Savezni Epidemiološki Institut
Bulevar Jugoslovenske Armije 16
Belgrade

in collaboration with

Dr. Jelka Vesenjak
Institute of Microbiology
University of Zagreb
Zagreb

South-East Asia Region

INDIA

Dr. I. G. K. Menon
Pasteur Institute of Southern India
Coonoor

Dr. D. W. Soman
Haffkine Institute
Parel
Bombay 12

Western Pacific Region

AUSTRALIA

Dr. W. J. O'Connor
The Commonwealth Serum Laboratories
Department of Health
Parkville, Victoria

in collaboration with

Sir Macfarlane Burnet
Walter and Eliza Hall Institute for Medical Research
Melbourne

JAPAN

Dr. Saburô Kojima
National Institute of Health of Japan
Tokyo

Annex 2

WHO INFLUENZA OBSERVERS

American Region

BOLIVIA

Instituto Nacional de Epidemiologia
La Paz

DOMINICAN REPUBLIC

Dr. J. J. Ravelo
Laboratorio de Salud Publica
Secretaria de Estado de Sanidad y Asistencia Publica
Ciudad Trujillo

ECUADOR

Instituto Nacional de Higiene
Guayaquil

Eastern Mediterranean Region

PAKISTAN

Dr. M. M. Siddiq Husain
Bureau of Laboratories
Military Hospital
Karachi

South-East Asia Region

CEYLON

Dr. K. G. B. Stork
Medical Research Institute
Colombo 9

Western Pacific Region

FEDERATION OF MALAYA

Dr. S. R. Savoor
Institute for Medical Research
Kuala Lumpur

NEW ZEALAND

Dr. F. S. MacLean
Division of Public Hygiene
Department of Health
Wellington

Sir Charles Hercus, D.S.O., O.B.E.
University of Otago Medical School
King Street
Dunedin, C.1

Dr. Selwyn Hills
Auckland Hospital
Auckland

PHILIPPINES

Division of Laboratories
Department of Health
Manila

Annex 3

WHO REGIONAL OFFICES

Address	Telegraphic address
World Health Organization Palais des Nations Geneva Switzerland	UNISANTE, GENÈVE
Regional Office of the World Health Organization for the Americas 1501, New Hampshire Avenue, N.W. Washington 6, D.C. USA	OFSANPAN, WASHINGTON
Regional Office of the World Health Organization for Eastern Mediterranean P.O. Box 1517 Alexandria Egypt	UNISANTE, ALEXANDRIA
Regional Office of the World Health Organization for South-East Asia Patiala House Hardinge Avenue New Delhi India	WORLDHELTH, NEW DELHI
Regional Office of the World Health Organization for the Western Pacific P.O. Box 2932 Manila Philippines	UNISANTE, MANILA
Regional Office of the World Health Organization for Africa P.O. Box 6 Brazzaville French Equatorial Africa	UNISANTE, BRAZZAVILLE
Regional Office of the World Health Organization for Europe Palais des Nations Geneva Switzerland	UNISANTE, GENÈVE

RÉSUMÉ

La grippe ne connaît pas de frontières. Une épidémie qui éclate dans un pays n'est pas une menace pour lui seul, mais pour les Etats environnants et, en fait, pour le monde entier. Aussi est-il logique que l'OMS exerce son action coordonnatrice dans la lutte contre cette maladie.

Le souvenir de la pandémie de 1918-19 suffirait à lui seul à expliquer l'inquiétude que peut faire naître l'apparition possible d'une nouvelle épidémie, dans l'ignorance où l'on se trouve encore des causes et des conditions de variabilité du virus, que l'on sait très peu stable. Il y a d'autres raisons encore : la nature hautement infectieuse de la maladie, la rapidité avec laquelle elle se propage et le fait qu'elle ne paraît pas conférer d'immunité permanente. De plus, elle est relativement meurtrière, en particulier par ses complications pulmonaires; ses répercussions économiques sont considérables.

Les objectifs de l'OMS dans la lutte contre la grippe sont les suivants : prendre des dispositions en prévision d'une éventuelle pandémie; établir des méthodes de lutte permettant de limiter l'extension et la gravité de la maladie ainsi que l'ampleur de ses répercussions économiques. Ces divers problèmes sont en relation étroite avec des questions techniques concernant les diverses variétés de virus, la variabilité de leurs caractères antigéniques, de leur pouvoir infectieux et de leur virulence. Il résulte des faits aujourd'hui connus que, pour être efficace, un vaccin contre le virus A doit être préparé à partir d'un virus étroitement apparenté à celui qui cause l'épidémie, qu'une vigilance constante est nécessaire afin de dépister le plus tôt possible les virus dangereux. Il s'agit avant tout de connaître dans le plus bref délai possible les caractères du virus responsable d'une épidémie, en particulier ses caractères antigéniques. Cette nécessité avait été reconnue en 1941 déjà par l'armée américaine. A cette date, la US Armed Forces Commission on Influenza établit un laboratoire central de référence — Strain Study Center — en relation avec des laboratoires régionaux pour l'isolement et l'étude des virus grippaux. Puis, en 1947, la Commission Intérimaire de l'OMS, répondant aux vœux de divers pays, décida la création d'un Centre mondial de la Grippe, établi à Londres, et l'organisation d'un réseau mondial de laboratoires. Le Strain Study Center des Etats-Unis accepta d'être désigné comme centre pour les Amériques, et il remplit pour le continent américain le rôle que le centre de Londres joue pour le reste du monde. Il y a actuellement 54 centres de la grippe désignés par l'OMS, dont 27 en Europe, 11 en Amérique du Nord, 6 en Amérique centrale et Amérique du Sud, 2 dans la Région de la Méditerranée orientale, 3 dans la Région africaine, 2 dans la Région de l'Asie du Sud-Est et 3 dans celle du Pacifique occidental. Bien que d'autres laboratoires collaborent à titre officieux, le réseau n'est pas encore assez étendu; la désignation d'« observateurs » dans diverses parties du monde est une des solutions qu'a adoptées l'OMS pour développer son réseau d'information sur la grippe. Les fonctions d'un centre de la grippe sont de deux ordres :

a) Notifier en toute hâte l'apparition de cas de grippe dans un pays, avec une première estimation de leur extension et de leur gravité. Ces renseignements devraient être donnés non tant par des chiffres précis que par un indice de morbidité grippale qui permettrait de se rendre compte de l'évolution d'une épidémie; il pourrait être établi, par exemple, d'après le taux d'absentéisme parmi les agents des entreprises de transports, les ouvriers d'usine, les écoliers.

L'annonce d'une épidémie est très souvent transmise à l'OMS par un centre de la grippe sinon par les services sanitaires; elle est suivie de rapports sur les travaux de laboratoire. Les informations sont transmises par les publications hebdomadaires distribuées dans le monde entier, par avion, de Genève, Alexandrie, Singapour et Washington, et, en cas d'épidémie, par télégrammes et bulletins radiodiffusés.

b) Identifier le type de virus en cause, par des réactions sérologiques et, si possible, l'isolement du virus. Ce dernier est envoyé immédiatement aux laboratoires intéressés, afin que, le cas échéant, des vaccins prophylactiques puissent être préparés dans divers pays. Les virus sont étudiés et comparés avec d'autres souches précédemment isolées.

La genèse des épidémies doit aussi être étudiée, car les mesures de lutte à prendre pour l'avenir en dépendent. Elle peut être géographique, l'épidémie se propageant à partir d'un centre d'origine — ce qui donne aux régions plus éloignées le temps nécessaire pour préparer un vaccin et protéger quelques groupes de la population. Elle peut, au contraire, apparaître simultanément en divers points, ce qui supprime toute possibilité de prophylaxie efficace. Il est évident que les recherches épidémiologiques ne peuvent être menées à bonne fin que par la collaboration internationale.

Un autre aspect de l'activité de l'OMS dans ce domaine a été l'établissement d'un groupe d'experts qui donnent des avis techniques sur les méthodes d'étude des souches, le diagnostic au moyen des épreuves de fixation du complément et d'inhibition de l'hémagglutination, la thérapeutique de la pneumonie grippale, etc.

En outre, les centres de la grippe ont entrepris des recherches sur d'autres maladies à virus, de sorte que le réseau de laboratoires pourrait s'adapter à des études de virologie différentes, si des problèmes internationaux de santé publique devaient brusquement l'exiger.

Depuis que cette organisation existe, les connaissances relatives à la grippe se sont considérablement développées, et l'on peut prévoir que l'on sera un jour en mesure de limiter les effets d'une éventuelle pandémie de grippe.

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ILLUSTRATIONS *

* The illustrations were kindly provided by the Statens Seruminstitut, Copenhagen (fig. 1), the World Influenza Centre, London (fig. 2 and 3), and the Institut Pasteur, Paris (fig. 4-21) ; fig. 11-21 are reproduced by courtesy of Dr. B. Fauconnier, Institut Pasteur, Paris.

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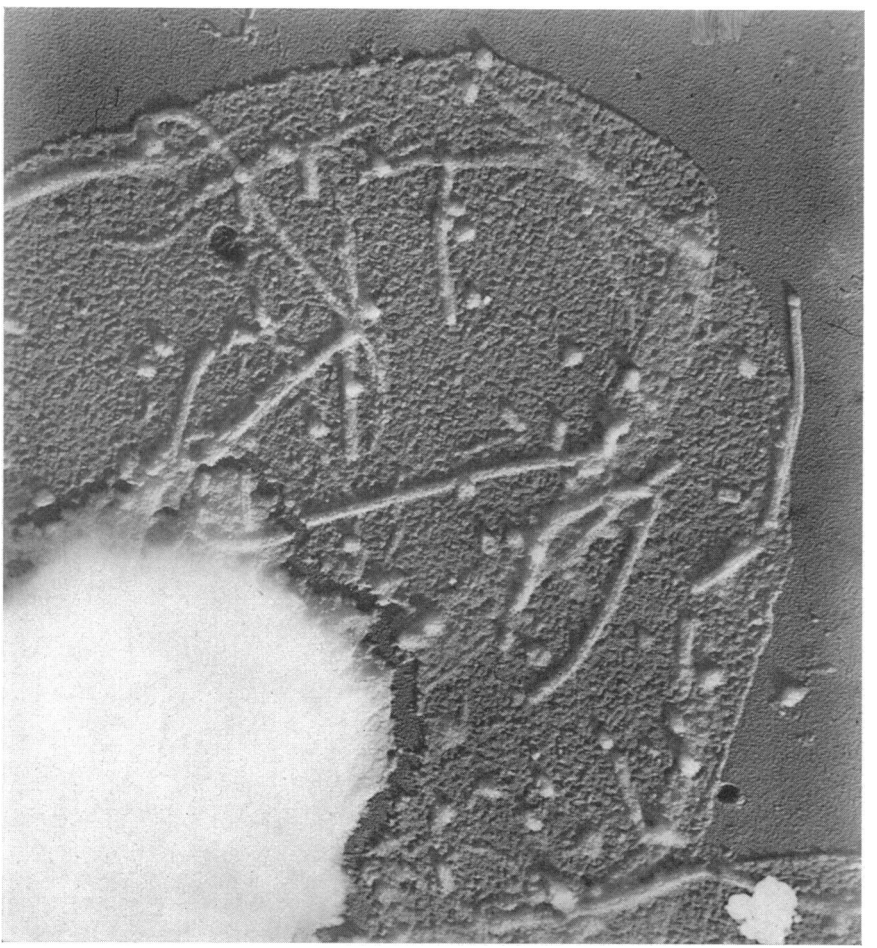
FIG. 1. VIRUS A (DAN/1/50) - ELEMENTARY BODIES AND FILAMENTS
Adsorption onto fowl red-cell ghost

VIRUS A (DAN/1/50) - CORPUSCULES ÉLÉMENTAIRES ET FILAMENTS
Adsorption sur stroma d'hématie d'oiseau



Palladium-shadowed

Imprégnation au palladium

FIG. 2. VIRUS A (ENG/1/51) - ELEMENTARY BODIES AND FILAMENTS
Adsorption onto fowl red-cell ghost

VIRUS A (ENG/1/51) - CORPUSCULES ÉLÉMENTAIRES ET FILAMENTS
Adsorption sur stroma d'hématie d'oiseau

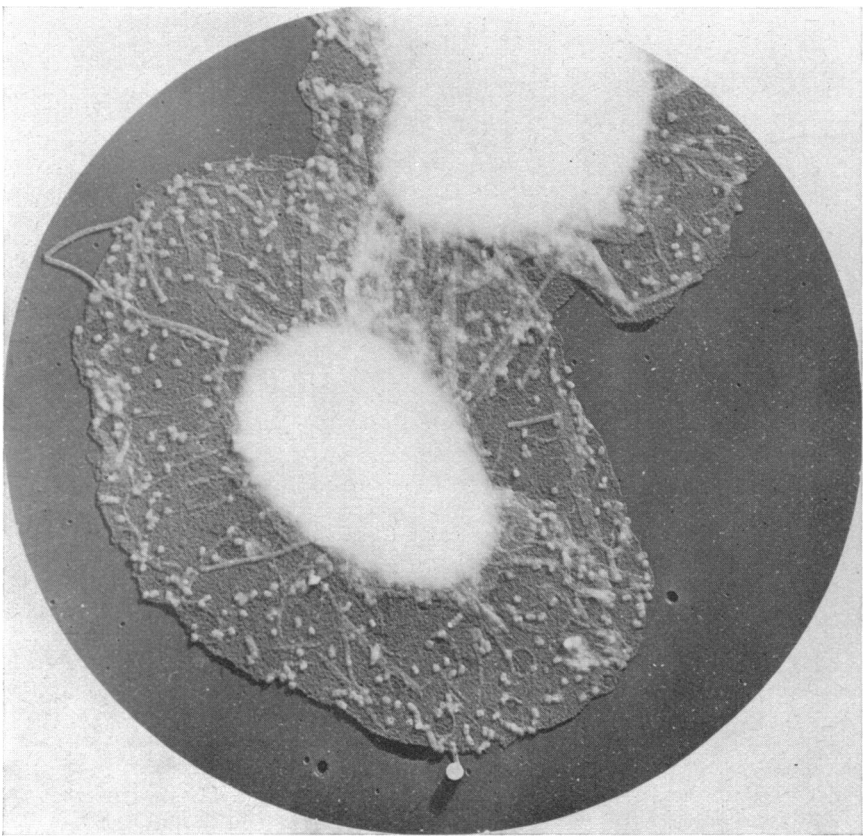


FIG. 3. VIRUS B (LEE) - ELEMENTARY BODIES
Adsorption onto fowl red-cell ghost

VIRUS B (LEE) - CORPUSCULES ÉLÉMENTAIRES
Adsorption sur stroma d'hématie d'oiseau

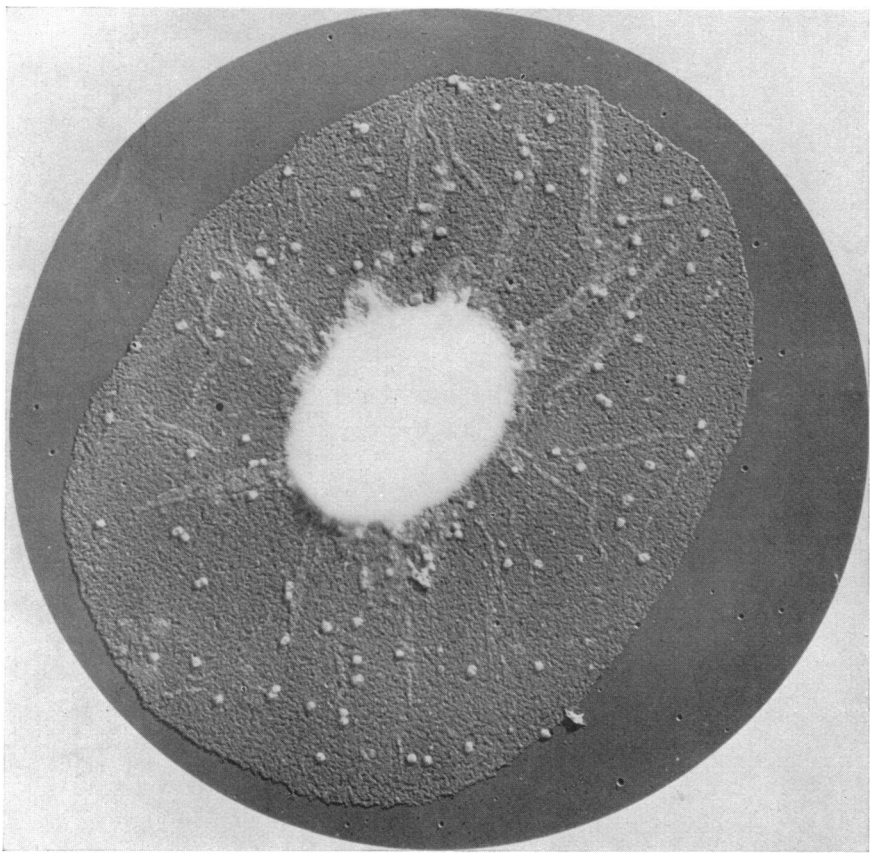


FIG. 4. VIRUS A (PR8) ADSORBED ONTO FOWL RED-CELL GHOST

VIRUS A (PR8) ADSORBÉ SUR STROMA D'HÉMATIE D'OISEAU

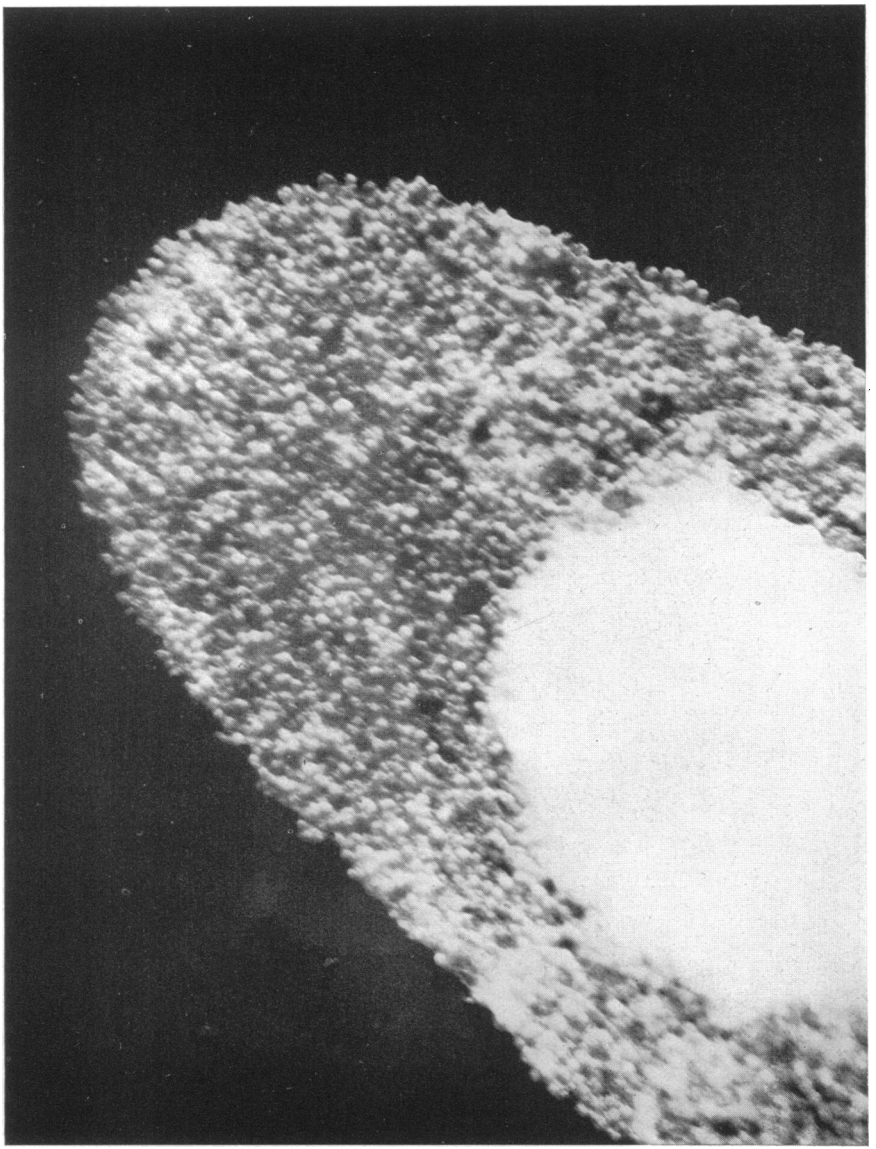
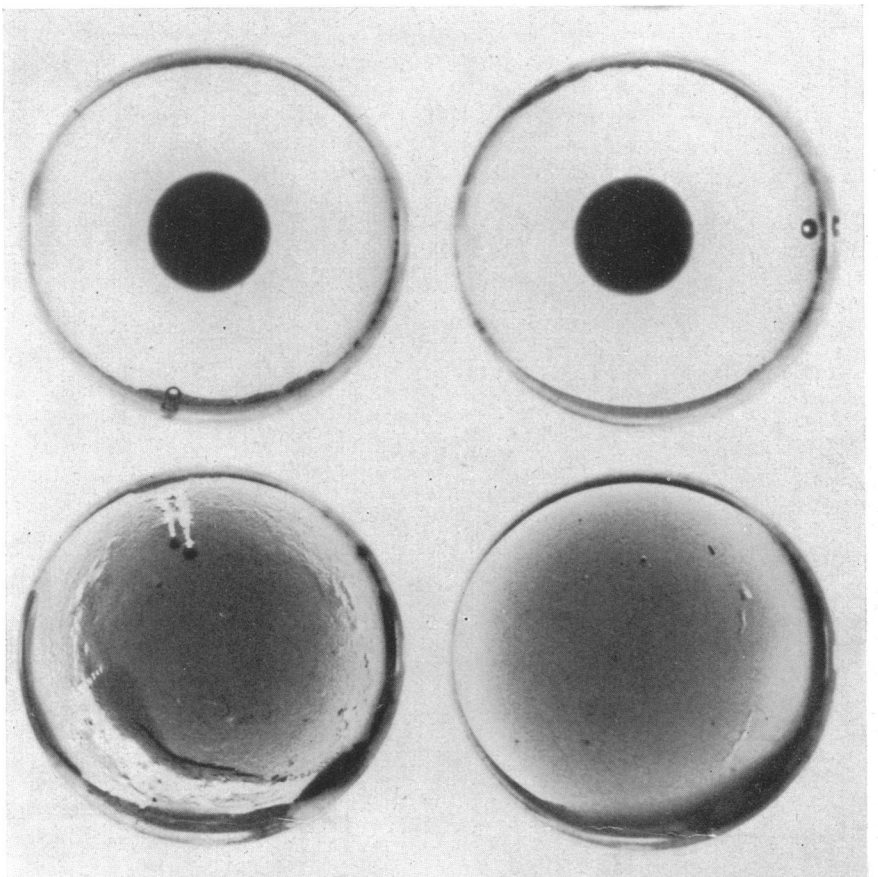


FIG. 5. HAEMAGGLUTINATION BY SPECIFIC SERA

HÉMAGGLUTINATION PAR LES SÉRUMS SPÉCIFIQUES



A — Negative ; natural sedimentation of red cells in the centre of the bottom of the tube

Négative ; sédimentation naturelle des hématies au centre du fond du tube

B — Positive ; agglutination of red cells covering the bottom of the tube

Positive ; hématies agglutinées garnissant tout le fond du tube

As seen in a mirror inclined at 45°
Vu dans un miroir incliné à 45°

FIG. 6. HAEMAGGLUTINATION BY SPECIFIC SERA
Series of reactions on a plastic plate

HÉMAGGLUTINATION PAR LES SÉRUMS SPÉCIFIQUES
Série de réactions sur plateau de matière plastique

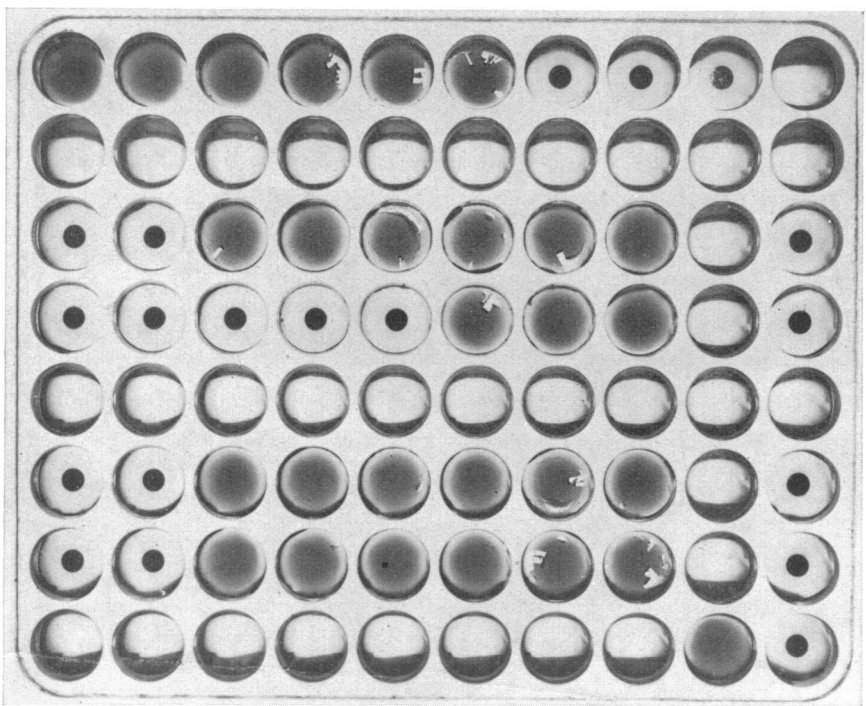


FIG. 7. TRACHEAL WASHING FROM MOUSE — I
24 hours after inoculation - normal cells

LAVAGE TRACHÉAL DE SOURIS — I
24 heures après inoculation - cellules normales

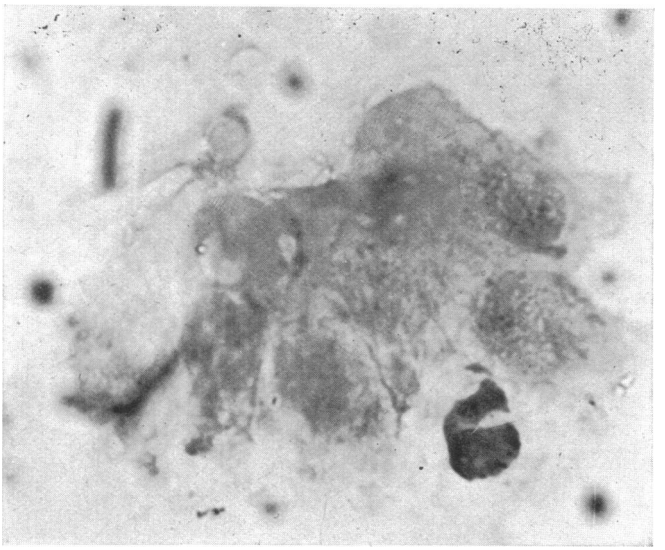


FIG. 8. TRACHEAL WASHING FROM MOUSE — II
48 hours after inoculation - infected cells

LAVAGE TRACHÉAL DE SOURIS - II
48 heures après inoculation - cellules infectées

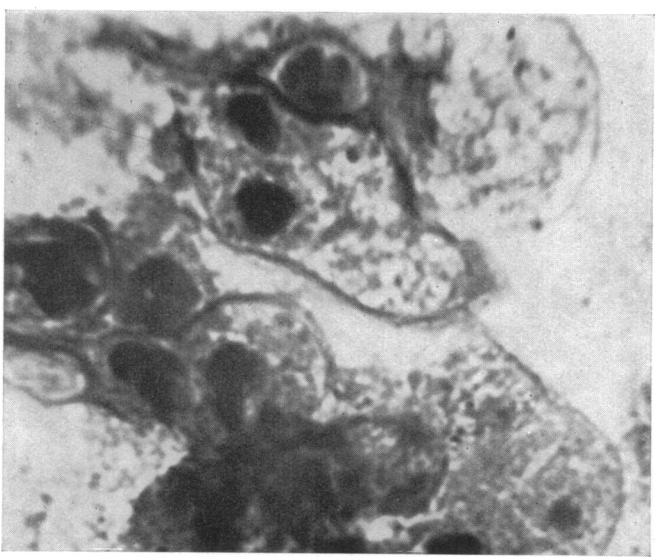


FIG. 9. TRACHEAL WASHING FROM MOUSE — III
72 hours after inoculation - intracellular bodies

LAVAGE TRACHÉAL DE SOURIS — III
72 heures après inoculation - corpuscules intracellulaires

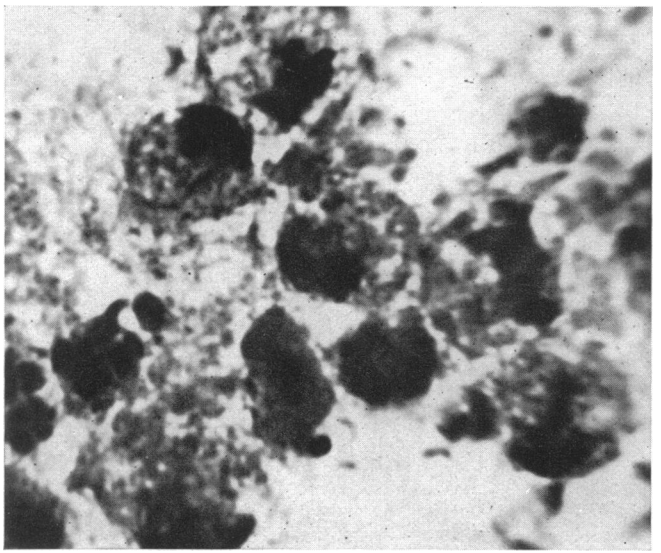


FIG. 10. TRACHEAL WASHING FROM MOUSE — IV
Four days after inoculation - ruptured cell

LAVAGE TRACHÉAL DE SOURIS — IV
Quatre jours après inoculation - cellule éclatée

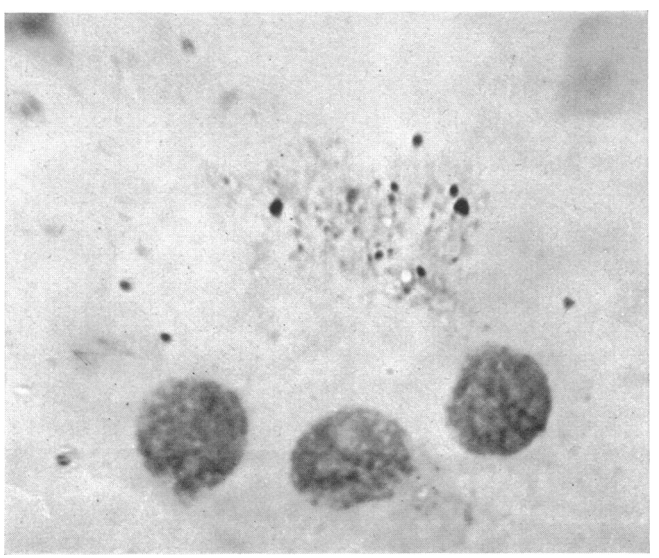


FIG. 11. TRACHEAL LAVAGE OF MOUSE
LAVAGE TRACHÉAL DE LA SOURIS

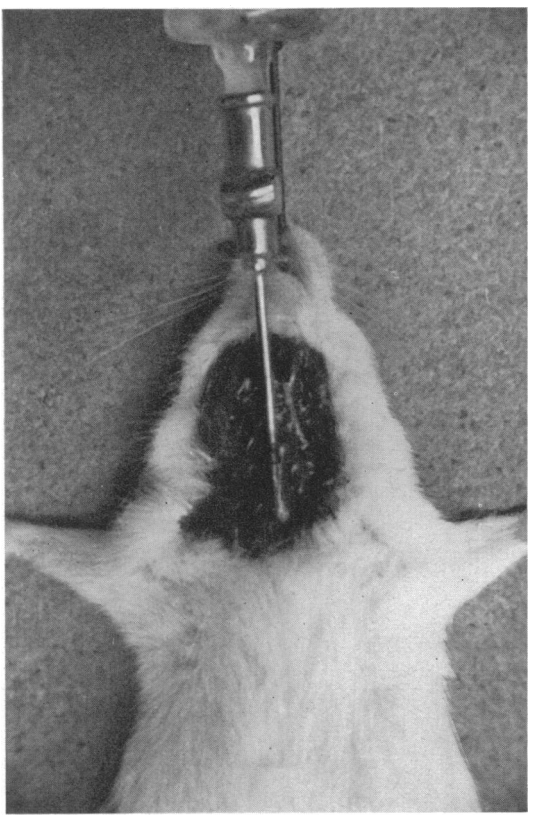


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FIG. 12. INOCULATION OF AMNIOTIC SAC — I
Opening of shell

INOCULATION DANS LE SAC AMNIOTIQUE — I
Ouverture de la coquille

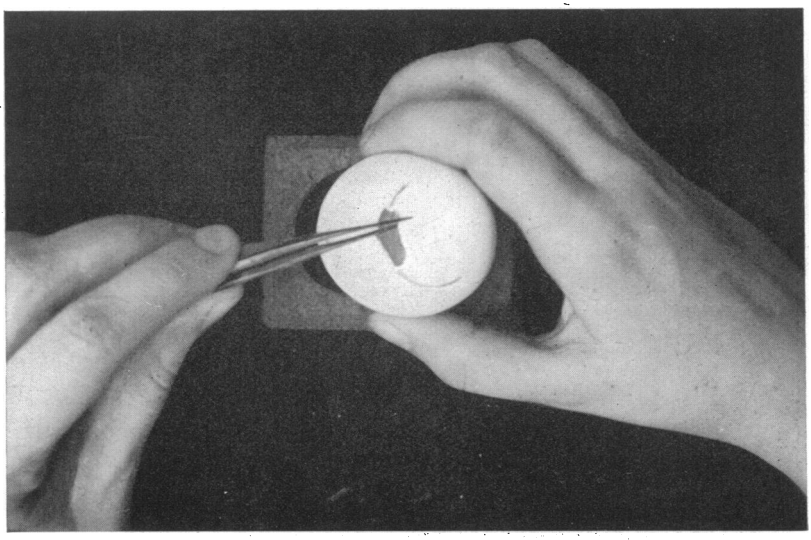

FIG. 13. INOCULATION OF AMNIOTIC SAC — II
Introduction of virus

INOCULATION DANS LE SAC AMNIOTIQUE — II
Introduction du virus

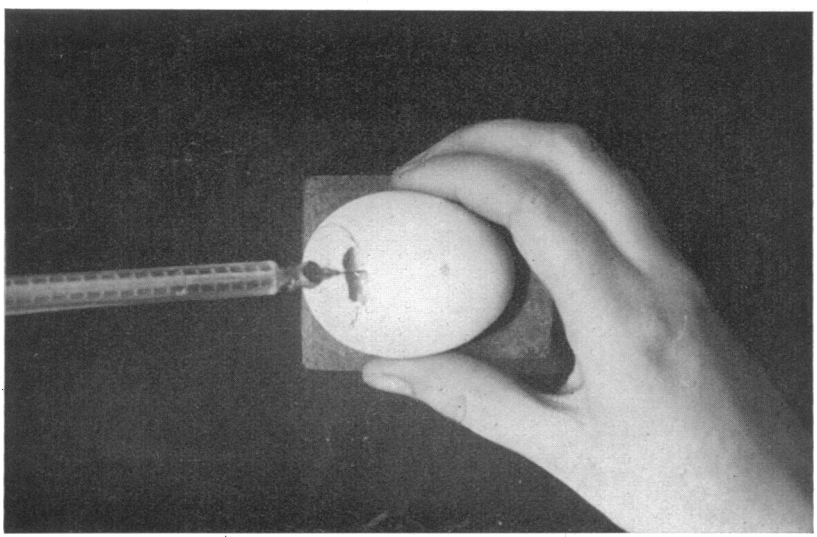

FIG. 14. INOCULATION OF AMNIOTIC SAC — III
Sealing with sterile cellophane tape

INOCULATION DANS LE SAC AMNIOTIQUE — III
Fermeture avec cellophane adhésive stérile

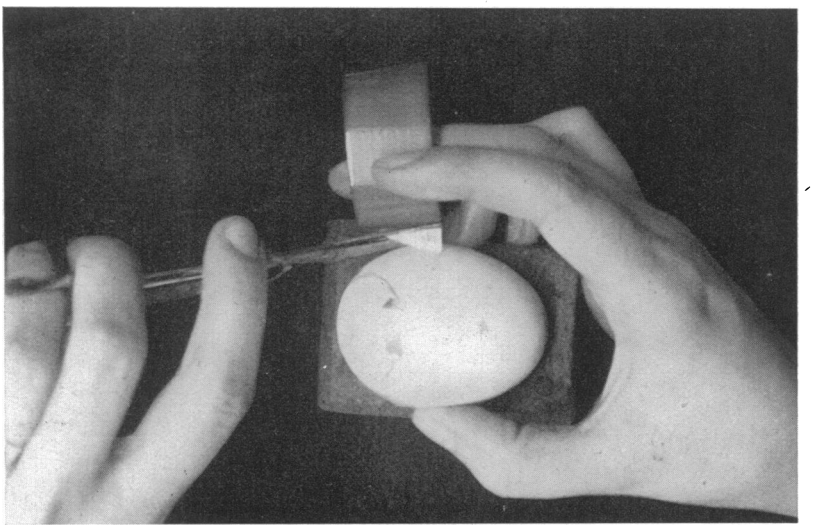

FIG. 15. TRAY OF EGGS READY FOR ALLANTOIC INOCULATION

PLATEAU D'ŒUFS PRÊTS POUR L'INOCULATION ALLANTOÏQUE

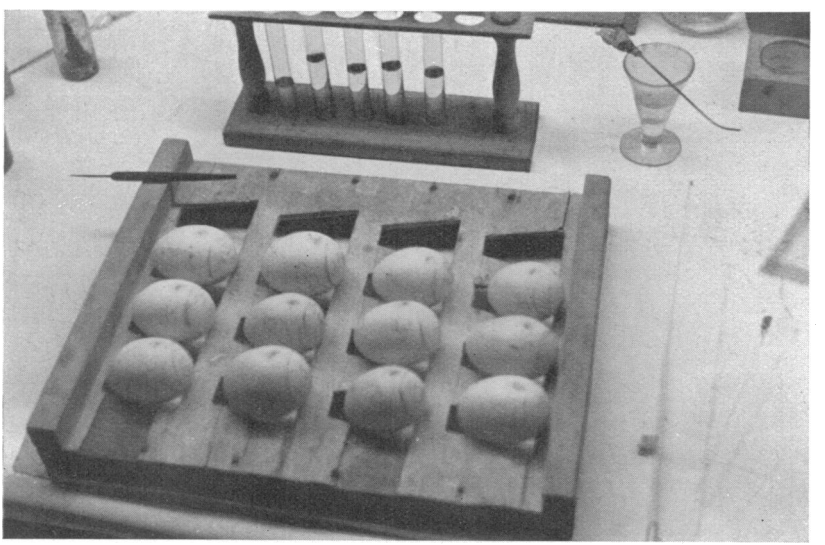

FIG. 16. INOCULATION IN ALLANTOIC CAVITY
INOCULATION DANS LA CAVITÉ ALLANTOÏQUE

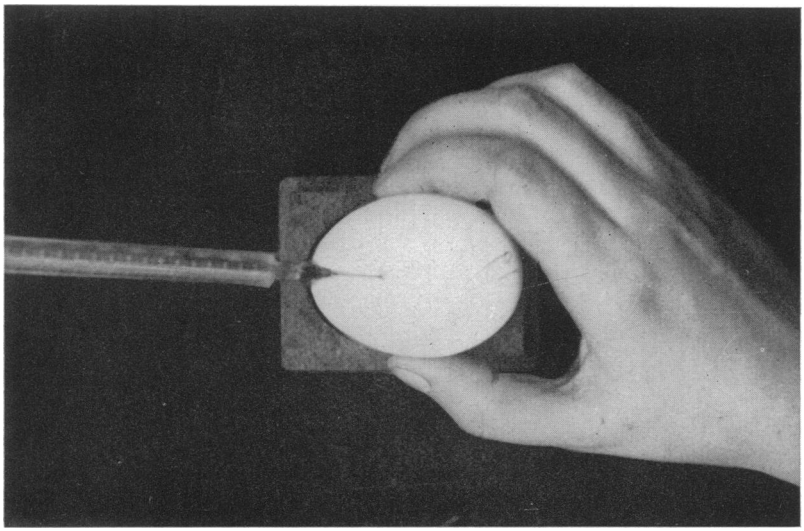

FIG. 17. WITHDRAWAL OF ALLANTOIC FLUID — I
Opening of air sac

PRÉLÈVEMENT DU LIQUIDE ALLANTOÏQUE — I
Ouverture de la chambre à air

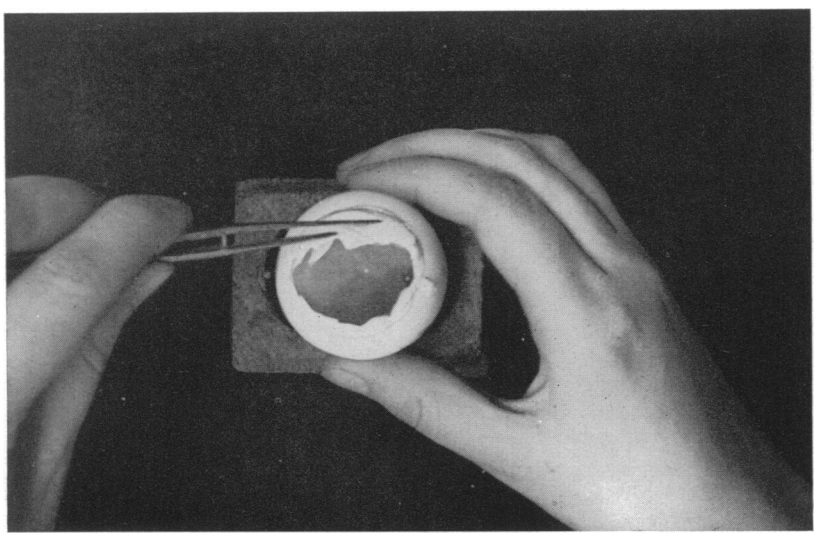

FIG. 18. WITHDRAWAL OF ALLANTOIC FLUID — II
Excision of chorio-allantoic membrane

PRÉLÈVEMENT DU LIQUIDE ALLANTOÏQUE — II
Découpage de la membrane chorio-allantoïque

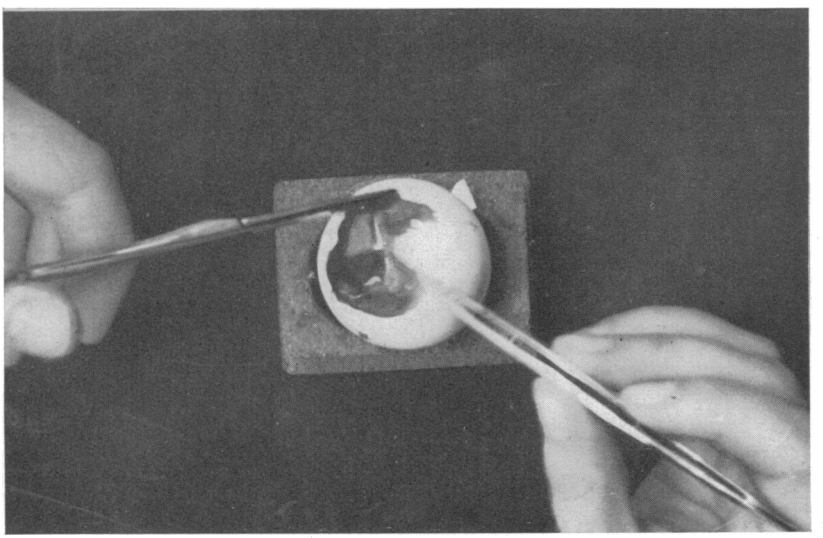

FIG. 19. WITHDRAWAL OF ALLANTOIC FLUID — III
Aspiration

PRÉLÈVEMENT DU LIQUIDE ALLANTOÏQUE — III
Aspiration

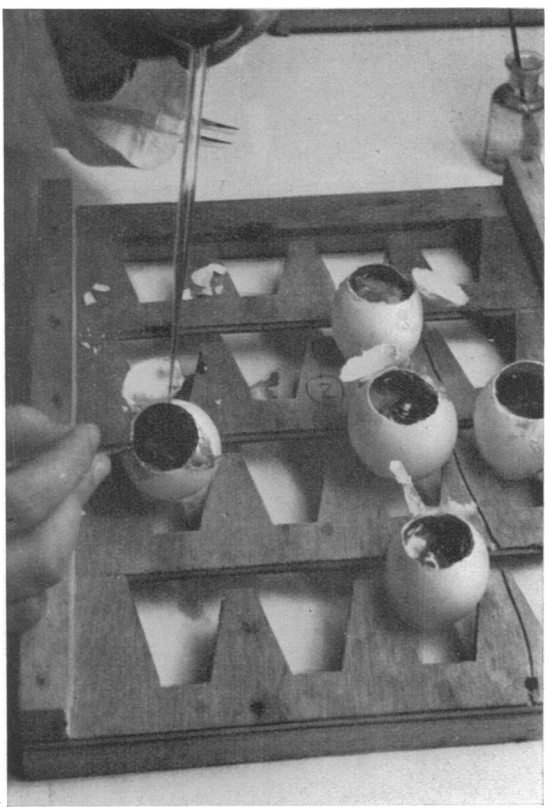

FIG. 20. INOCULATION OF EMBRYONATED EGG WITH MOUSE BLOOD — I
Puncture of mouse heart

INOCULATION DU SANG DE LA SOURIS A L'ŒUF EMBRYONNÉ — I
Ponction du cœur de la souris

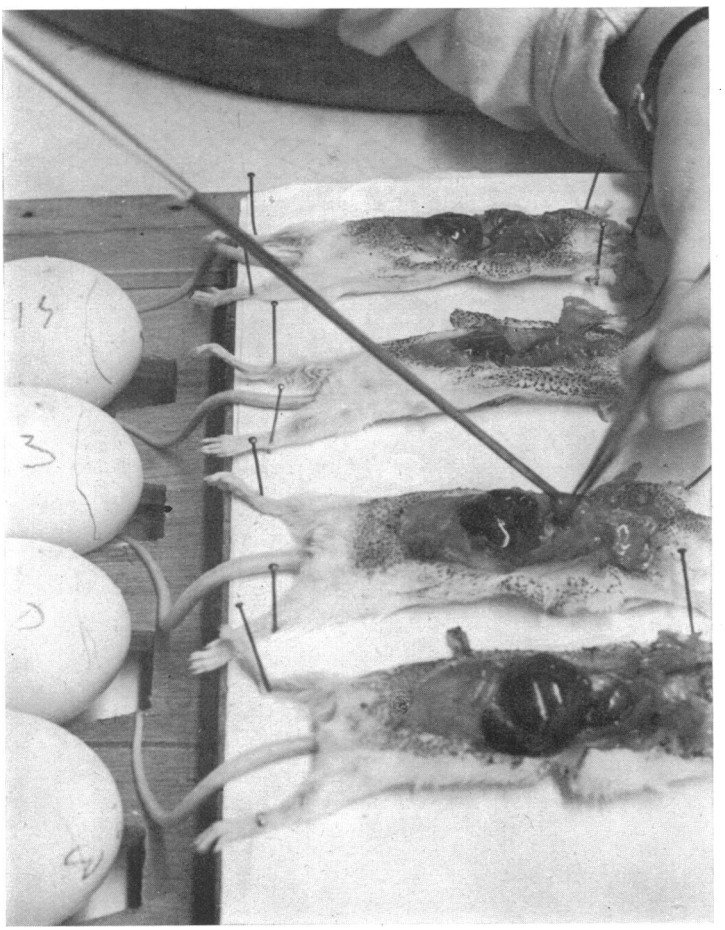

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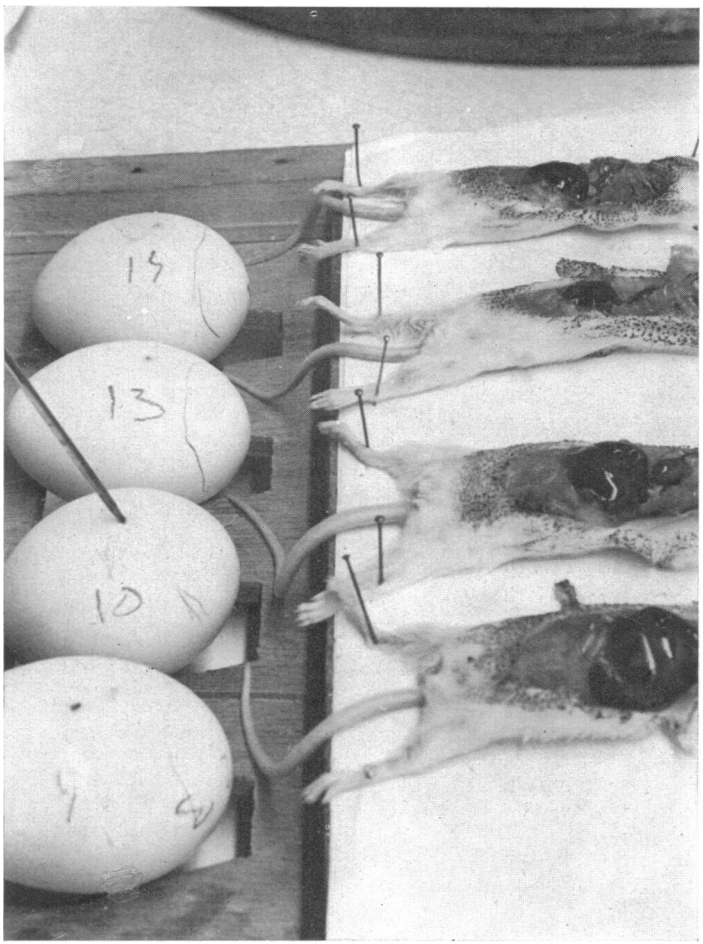
FIG. 21. INOCULATION OF EMBRYONATED EGG WITH MOUSE BLOOD — II
Immediate inoculation of egg

INOCULATION DU SANG DE LA SOURIS A L'ŒUF EMBRYONNÉ — II
Inoculation instantanée à l'œuf



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