RECENT RESEARCH IN FOOT-AND-MOUTH DISEASE*

[This article may be regarded as a brief summary of recent research as outlined in the Fourth Progress Report of the Foot-and-Mouth Disease Research Committee, including reference to work described in earlier Reports.]

THE existing Committee for Research on Foot-and-Mouth Disease was appointed by the Minister for Agriculture and Fisheries in March, 1924, and it has issued four reports.

When the work of the Committee began, certain fundamental problems regarding the disease were still unsettled, since effective research on the subject had only been carried on at a few centres abroad, and in several instances the conclusions of different workers had been contradictory.

A great advance was made in the methods of investigating the disease when in 1921, Waldmann and Pape, working at the isolation station for foot-and-mouth disease research on the Island of Reims in Germany, made the valuable discovery that guinea-pigs could be infected with foot-and-mouth disease regularly if the virus was inoculated on the under surface of the foot, i.e., the plantar pad. A minute inoculation at this spot reproduces the disease which manifests itself by vesicles at the site of the inoculation and on the tongue, lips and other feet, as in cattle. This discovery made research into the disease very much easier and less expensive, since the inoculation of guinea-pigs can now be used to detect the presence of active virus and to estimate its strength.

Up to this time the suggestion that guinea-pigs, rats and other small animals might contract foot-and-mouth disease was regarded as very unlikely, since many unsuccessful attempts had been made to infect them experimentally. There are great inherent difficulties in working with farm animals that are costly to buy, to feed and to look after, and that need a large space. All experiments, therefore, that can be performed on such animals as the guinea-pig, are best carried out on them.

The virus of foot-and-mouth disease was the first infective agent of the kind to be recognized. Loeffler and Frosch made the discovery in 1892 that the serious fluid or lymph taken from a vesicle on the tongue of a calf could be diluted 40 times with water and passed through a Berkefeld filter that kept back all ordinary bacteria, and that the resulting liquid was infective for a calf in a dose of one cubic centimetre (about 20 drops), injected into a vein, and further that lymph might be diluted 5,000 to 20,000 times and still produce the disease in calves. The particles of this virus are so small that they will not only pass through finer filters than those of almost every other virus, but are quite invisible with the highest powers of the microscope.

Like most other viruses that the foot-and-mouth disease cannot be cultivated on artificial culture media as can ordinary bacteria. The exact strength and activity of a sample of a virus can be estimated by inoculating guinea-pigs with different dilutions of the virus and determining the highest

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dilution with which infection can be obtained. A good sample of vesicle fluid will still infect a guinea-pig after it has been diluted with water 500,000 or 5,000,000 times. By estimating the strength in this way the survival or rate of destruction of the virus under different conditions can be accurately measured. Experiments have shown that the virus in vesicle fluid or blood, even when diluted, will withstand rapid drying and if kept chemically dry may remain active for as long as two years. Exposed to the air and allowed to dry, the virus does not, as a rule, remain infective very many days. If vesicle fluid is dried in this way in the open air on blotting paper or wooden articles, the survival does not exceed one or two weeks, but on some substances (such as leather), and especially on certain articles of fodder (such as hay and bran), active virus has been found to persist for a very much longer time at ordinary temperatures.

At a temperature of 122° to 140°F., the virus is killed in a few minutes and sunlight is also very destructive.

Disinfectants.—Experiments with disinfectant liquids under conditions as far as possible like those met with in practice show that carbolic and cresylic acids and similar materials are less powerful against the virus than against most bacteria. A 4 per cent. solution of common washing soda in water was found to be the most practical disinfectant. A solution in hot water at 140°F. can be used effectively for washing butchers' utensils and for scrubbing tables and floors of slaughterhouses. A 1 per cent solution of caustic soda is also a very useful disinfectant and is much used in Germany. The disinfection of hides requires special care since many disinfectants spoil the leather. Immersion in a solution of 1 part bisulphate of sodium in 10,000 of water for five hours or of 1 of sodium fluoride in 20,000 of water for two hours killed the virus and did not damage the hide.

Distribution of the Virus in the Animal Body.—When a cow has been inoculated with virus by scratching or by injecting a minute quantity into the thickness of the mucous membrane of the lip or tongue, a period of incubation follows, usually lasting three or four days. A vesicle then appears at the site of inoculation and one or two days later secondary vesicles also break out in the mouth and on the feet. In guinea-pigs, the incubation is usually only 24 hours after inoculation on the sole of the foot. The distribution of the virus in the body of an infected animal has been carefully studied. It has been found, that in cattle, the time between infection and the presence of the virus in the blood is usually three to five days, but in the guinea-pig only one or two days; but the maximum infectivity of the blood is usually reached about the time when secondary vesicles first appear, or shortly before, and then it rapidly decreases, until after the full outbreak on the feet and mouth the blood has almost ceased to be infective. The skin or mucous membrane at the sites of the vesicles has been found to retain active virus longest, but even here it can seldom be detected for more than 10 days in cattle, or a week in the guinea-pig, from the onset of the disease. During the first few days the milk and urine are usually infected, like the blood, and the virus is also present in the internal organs and bone-marrow, but disappears from them also when it leaves the blood.

Persistent Infectivity of the Live Animal.—Some observers maintain that cattle that have passed through an attack do not all rid themselves of the virus so readily, but that a very few remain infectious for months. Whether such persistent "carriers" of the virus really occur is not yet finally settled.

Duration of Infectivity of the Carcass.—Although during life an animal usually rids itself of the virus rapidly and completely, if it is killed at the height of the disease the carcass may remain infectious for a very long time.

Direct experiments have shown that carcasses of cattle killed and dressed by trade methods remain infective when kept frozen or chilled for long periods.

Effect of Storage at Different Temperatures on the Infectivity of Carcasses.—In view of the importance of the persistence of infectivity in stored carcasses, experiments have been made on the carsasses of cattle and guinea-pigs. The virus was recovered from the bone-marrow of carcasses of guines-pigs killed at the height of the disease after the carcasses had been kept for 13 days at 64°F. and had become partly putrid. Other experiments have shown that the virus usually remains active for very much longer periods when carcasses are kept at "chilling" or freezing temperatures. It is known that freezing and thawing has the effect of killing some bacteria, but it has been found that repeated freezing and thawing has little or no effect in lessening the activity of the virus. In order to test more exactly the conditions under which carcasses are kept when stored for trade purposes, cattle were allowed to acquire infection by contact with other animals and were slaughtered by a butcher at the stage of the disease which was believed to be the most infective. The results of experiments made with 10 cattle show that if animals at a highly infective stage of foot-and-mouth disease are killed, dressed, and stored at a "chilling" or freezing temperature they may remain infective for some weeks.

Resistance of the Virus to Pickling.—Not only does the virus survive in the carcass kept in the refrigerator, but it has been found that parts of a carcass may still be infective after preservation in pickling solution of salt, etc. Virus in the feet of infected guinea-pigs remained active in different pickling solutions for periods up to 35 and 49 days.

Milk.—The use of the milk of the infected cows is believed to be a common means of spreading the disease on the Continent, since if it is not heated, milk may infect calves or pigs fed on it. The time during which, virus will survive in milk depends on the circumstances, and especially on the temperature. The virus is soon killed when the milk becomes sour.

Dried Milk.—Milk powder is usually made by drying on a heated roller or by spraying milk into a dry and heated chamber. Experiments suggest that the virus may not be killed by the spraying method if the milk has not previously been sterilized by heat; but that drying on heated rollers is much more likely to do so.

Types of Virus.—One attack of foot-and-mouth disease generally protects an animal against further attacks for at least one or two years. Practical experience on the Continent has shown that cattle occasionally have two or more attacks of the disease within a few months and this has been explained by the discovery in1922 that there is more than one type of virus. Each type causes an attack of foot-and-mouth disease, but the attacks due to two distinct types of virus do not protect the one against the other. Three distinct types are known, O and A described by Vallee, and C by Waldmann, and there is evidence that others exist. The three known types of virus produce similar attacks of disease. The only way of discovering the types to which a newly-acquired strain belongs is by inoculating with it animals immune to known types of virus in order to see whether they are susceptible to the new strain. In all, 40 strains have been examined from outbreaks in this country, and of these 37 conformed to the O type.

Foot-and-Mouth Disease in other Animals besides Cattle, Pigs, Sheep and Coats.—(1) *Man.*—The occurrence of foot-and-mouth diseases in man has seldom been conclusively proved, but two undoubted accidental infections of laboratory workers have been recorded.

(2) *Rats.*—The infection of the wild rats can be obtained by inoculation, and they can also be infected by feeding them with virus from Guinea-pigs. Rats caught on a farm in Yorkshire, the site of a foot-and-mouth disease outbreak, were noticed to have suspicious sores and were sent to the Ministry's Laboratories at Pirbright for examination. Material from one of these rats was inoculated into a guinea-pig and produced definite foot-and-mouth disease. virus was also obtained from a rat caught at the experimental station at Pirbright; from this, guinea-pigs, wild and albino rats and swine have been infected. Swine have also been infected by feeding them on bodies of guinea-pigs inoculated with this strain of virus. The signs of infection in rats may be very slight, but include vesicles on the feet and toes, on the tongue and lips and on the tail. Altogether 132 rats have been caught at Pirbright and in the immediate vicinity of the compound, and six of these have been found to be infected.

(3) *Hedgehogs.*—Infection of hedgehogs has been repeatedly obtained by inoculating them with virus. After inoculation they usually become very ill and were killed or died in a week or ten days. Healthy hedgehogs kept in contact with those recently inoculated also showed signs of severe infection. The virus recovered from hedgehogs was highly infective for guinea-pigs. The hedgehog is the only species of animal, besides farm animals, in which rapid spread of a severe form of the disease by contagion is known to occur, though it has also been found that the transmission by contact may occur fairly often among rats in captivity.

(4) *Rabbits, Dogs and Cats* have all been infested in the laboratory, but scarcely anything is known of cases occurring naturally, and the disease has not been shown to spread readily among these animals.

Virulence and Adaptation of the Virus.—(1) *Virulence.*—It is a common experience in infectious disease, whether due to bacteria or a virus, that the infective agent varies in activity at different times and in different conditions and epidemics. A strain of foot-and-mouth disease virus of low activity can often be restored to full virulence by rapid infection of one susceptible animal after another by direct transmission.

(2) *Adaptation.*—In attempted transmission of the disease from one kind of animal to another even a very active virus may fail to infect the new species. Such a virus may often be adapted to the new kind of host by the inoculation of two or more individuals in succession with very large doses. In some outbreaks among swine or sheep, foot-and-mouth disease does not readily speard to cattle and *vice versa.* In a similar way certain strains of virus from cattle have only been adapted to guinea-pigs with great difficulty, and repeated inoculations with some such strains have failed to infect the latter animals. Observations on adaptation show how dangerous it is to conclude without prolonged trial that a given species is not susceptible to the disease or is not infective for another species.

Artificial Production of Immunity.—Four methods have been used with several variations to produce specific resistance against foot-and-mouth disease. (1) The injection into animals of the blood-serum of inoculated cattle gives some protection for about 10 days. It has been found useful in the case of animals exposed to infection in markets, shows, etc., but the appearance of the disease may only be delayed. The serum is prepared by Waldmann at Reims, and is said to be "hyperimmune" and "polyvalent" because the cattle from which it is taken have received several doses of each of the chief types of virus. An average of 200 cubic centimetres or about 6 oz. of serum is required to protect each adult bovine.

(2) Inoculation with active virus and at the same time with serum, so as to diminish the severity of the attack while not preventing it altogether, allows an animal to acquire the more lasting kind of resistance and usually

follows an attack of the disease. By this means the disease may be rapidly passed through all the cattle in a herd, but in some cases the eruption of vesicles is delayed by the serum given. The period of quarantine imposed in Prussia is about five weeks after the inoculation. Since the cattle inoculated by this combined method are infective for a time for other animals, all the cattle in their immediate neighbourhood are given a protective dose of serum in order to prevent them from becoming infected and so spreading the disease. In Germany this method is called the "Ringimpung" and is considered, especially in Prussia, to give very valuable results; but for various reasons the spread of disease and the renewed occurrence of outbreak is not always prevented.

(3) Several methods of inoculation with attenuated virus have been used at different times, in imitation of the vaccination of a man against small-pox, but no method of obtaining an attenuated virus that would be certain not to produce severe disease has yet been discovered.

(4) The inoculation of animals with virus that had been killed by treatment with formalin has been tried. A considerable degree of resistance can be regularly produced in this way, but it is necessary to use a very large amount of virus of the prevalent type and high potency, and this it may be difficult to obtain. It is important that such a vaccine should be prepared by an exact method and that it should be thoroughly tested both for loss of infectivity and for its protective power on guinea-pigs before it is used on cattle.

Sources of Infection.—Evidence adduced from long experience on the re-appearance of foot-and-mouth disease after slaughter and disinfection in England has recently been summarized. Out of 5,554 infected centres that have occurred in the course of the last 20 years, where re-stocking has taken place from 4 to 18 weeks after disinfection, the disease has re-appeared in 57 centres, though in 13 of these the disease was probably re-introduced. It has been pointed out that the material taken experimentally from animals at the height of the disease retains infectivity as a rule much longer than the flakes of epithelium, etc., thrown off naturally by the animal during recovery. The recovered animal also usually becomes rapidly disinfected. It has been found that infection was much more persistent in cow byres in winter. It has been claimed that affected cattle and the stalls in which they had been confined often ceased to be infective for fresh animals 4 or 5 days after the onset of the disease. This has been confirmed at Pirbright at all seasons of the year under experimental conditions.

Observation and research during the last eight or ten years have indicated certain sources of infection that, in addition to the possible occurrence of "carriers" especially demand further attention and experiment. These sources of infection may be placed in three categories:

(1) Foci of virus outside the animal body. The conditions needed for survival of the virus have been discussed in the Progress Reports and in the earlier pages of this summary.

(2) It has been shown that a wide range of animal species can be infected with foot-and-mouth disease. The transference of infection from one species to another does not always take place easily, and adaptation of the virus to the new species has sometimes to be acquired gradually before a well-marked infection occurs with regularity. The fact that the rats are susceptible, and the discovery that the signs of the disease in them may be very inconspicuous, must increase the care with which symptoms of infection in these animals are sought for, and adds fresh importance to the warfare waged against them. The nocturnal and unobserved habits of the hedgehog and its undoubted high susceptibility make further inquiries concerning this animal important.

(3) The carcasses of animals that have been killed during the infective period may contain deposits of active virus for long periods after they have been subjected to various pickling processes, or when they have been kept at low temperatures. Pigs can become infected by feeding on parts of such carcasses, especially on crushed bones. It is clear that this importation of infected meat or offals in the chilled or frozen state is a ready means by which infective material can be brought to this country, and that one way in which the infection may be transmitted to farm animals is by feeding pigs. Whether this source of infection is operative or not depends on the state of the animals at the time and place of slaughter and on how the carcasses are disposed of after arrival in this country.

Preventive and Curative Treatment.—Apart from inoculation with serum or vaccines, no special method of countering the infection by means of drugs have been discovered. Hyper-immune serum in large doses may reduce the severity of an attack. Many claims have been made that the disease can be prevented or an attack cut short by the injection of chemical substances, but none have so far stood the test of carefully controlled experiments. Very many chemical substances have been tested, but not one of them has been found to modify the course of the disease in doses that were not seriously poisonous to the animals. In conclusion, the following passage from the Fourth Progress Report may be quoted:

"It may be said with confidence that during the past two or three years the knowledge of foot-and-mouth disease, the conditions which promote the infection and the means for its prevention have been materially advanced by work in many parts of the world and that the research workers in this country have taken their fair share in furthering that progress."