The Danish State Veterinary Serum Laboratory

A Review of Past Achievements and Current Activities

By H. E. Ottosen

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Historical Data
The Danish State Veterinary Serum Laboratory was established in 1908. Its first director was Professor Carl Oluf Jensen**, who had for the past ten years been carrying out research on the possibility of combating infectious animal diseases by means of serum or vaccine.

This research had taken place in the then existing Bacteriological Department of the Agricultural Research Institute, where a special section, headed by Jensen, was set up for that purpose in 1898.

The duties of the new institute included research on infectious animal diseases as well as the production and distribution of sera, vaccines and other bacteriological products.

Since a correct diagnosis was a prerequisite for the rational use of sera and vaccines, the institute also had to establish a bacteriological diagnostic service to veterinarians. In 1922 this service was extended to include also diagnostic examinations required by the Government Veterinary Administration.

In 1932 a change took place in the administrative status of the institute, which had till then been a department under the Royal Veterinary College, but now became directly included under the Ministry of Agriculture.

Extensons of the laboratory in Copenhagen have taken place in 1916, 1933, and 1938. In 1949 a branch of the institute was...

*) D.V.Sc., Director.

**) Jensen was director until his death in 1934. He was succeeded by M. Christiansen, who retired in 1932. From 1932 to 1960 the post was held by N. Plum.
Established at Aarhus (Jutland) and in 1957 a mastitis laboratory at Ringsted (Zealand). Since 1929 the institute has had an experimental farm at its disposal. A major extension of the laboratory in Copenhagen is under way.

Present Organization

The institute is headed by a director, who is a veterinarian, and who is responsible directly to the Ministry of Agriculture. To his aid he has an administrative officer, who is a jurist. It has a staff of about 230 persons, including about 30 veterinarians and one chemist.

The scientific work is divided among a number of departments, each headed by an assistant director.

The responsibilities of the various departments are not sharply delimited, mainly because the work is not divided up by disciplines, but rather by species of animal and kind of disease, and to some extent also under consideration of the special knowledge and interest of individual staff members.

Below, the departments existing at present are listed and their main lines of activity indicated.

A. Main laboratory (Copenhagen)

I. Biologics production. Diagnosis of Vibrio fetus infections. Health control of bull semen. — Head: Dr. E. Blom.


III. Diseases of pigs, sheep, horses, cats, dogs, and furbearing animals. Production of mink-distemper avianised vaccine. — Head: Dr. Betty Knox.


V. Virus and Mycoplasma infections generally. Haematology. Bovine leukosis. — Head: Dr. H. J. Bondixen.

VI. Clinical biochemistry. Bovine mastitis. — Head: Dr. H. C. Hovmand.

B. Branch laboratory, Aarhus


II. Bovine mastitis.

III. Diseases of fish.

Head: Dr. J. Jørgensen.

C. Mastitis laboratory, Ringsted


Head: Dr. O. Klastrup.

D. Experimental farm

Housing of larger experimental animals and animals for serum production. Raising of large and small experimental animals. Production of food-stuffs.

Head: Mr. K. G. Frederiksen.

Past Achievements

In the following, a brief account is given of the most important scientific and practical results that have emanated from the work of the Serum Laboratory.

Cow mortality

Studies on diseases of young calves, initiated by Jensen already in the nineties, and continued and intensified when the Serum Laboratory came into being, led to the recognition of a number of septicaemic bacterial infections as causes of death in new-born and young calves, and to the development of effective antiserum against some of these infections, e.g., E. coli, Salm. dublin, and Diploc. pneumoniae infections.
After the Second World War, infections with Salmonella types other than dublin began to appear with increasing frequency among calves. *S. typhi-murium*, which had hitherto been found but rarely in calves, was now isolated in a considerable number of cases, and types previously quite unknown in this country turned up. Through research carried out at the Serum Laboratory it was demonstrated that the "exotic" types had been introduced with meat- and bone-meal of foreign origin.

Through a comprehensive study of strains of pneumococci isolated from cases of septicaemia in calves it was shown that the same serotypes occurred in calves as in human beings. This led to a suspicion of human carriers of pneumococci being a source of infection to calves, a suspicion which was eventually substantiated by the finding of identical types in farm-workers and calves on the same farms.

The question of environmental factors as a predisposing cause to calf mortality was investigated in the fifties. It appeared that, on an average, calf mortality was significantly higher in herds with moderate or low milk yields than in herds with high yields. This observation was considered to reflect the high standard of management which is a prerequisite for a high yield.

It also appeared that herds in which the adult stock was fed excessive amounts of root-crops suffered a significantly higher calf mortality than herds also fed reasonable amounts of other kinds of roughage (silage and/or hay).

In a histopathological study, also undertaken in the fifties, it was found that respiratory disorders in calves were in the majority of cases associated with lesions of the pneumonitis type. It was concluded, therefore, that pneumonia in calves was, to a wide extent, primarily of viral aetiology. Owing to lack of facilities it has not yet been possible to follow these findings up with virological studies.

**Diseases of swine**

Diseases of swine have not been studied so intensely at the Institute as diseases of calves. Yet, in the twenties a great deal of work was done in an attempt to clear up the aetiology of the respiratory and intestinal disorders occurring enzootically in many herds and causing great losses.

At the time it was generally believed that the respiratory disorder prevailing among swine in Denmark was identical with the disease known in Germany as Schweinescheuche, i.e., a pneumonia caused by *Pasteurella*, and that also the intestinal disorders were caused by some specific infection.

Through very thorough investigations it was shown, however, that true pasteurellosis was a rare disease in swine in Denmark, and it was concluded that most cases of pneumonia and enteritis were to be ascribed to unfavourable environmental conditions paving the way for infection with potentially pathogenic microorganisms of various kinds.

Later investigations revealed that iron deficiency was an important factor in the aetiological complex of many disorders in young pigs.

In the thirties research was carried out on the aetiology of swine enzootic pneumonia (at the time known as European swine influenza or, in Germany, *Ferkelgrippe*). It was demonstrated that the disease could be reproduced in pigs by nasal instillation of bacteria-free filtrates of extracts of diseased lungs, and that the presence of bacteria was not necessary for the filtrable agent to produce lesions.

Lately, a highly fatal necrotizing enteritis in piglets was found to be caused by *Cl. perfringens* type C.

**Brucellosis**

Two of the methods now in common use all over the world in the diagnosis of brucellosis, i.e., the tube agglutination test and the complement fixation test, were worked out at the Serum Laboratory in the early part of this century.

In the forties a method for intratival staining of *Brucella* ring-test antigen with tetrazolium salts was developed.

At about the same time extensive studies were commenced on the use of intradermal tests in the diagnosis of brucellosis. A new diagnostic agent was developed, which had the advantage over previously used brucellins that it was practically devoid of antigenecity and therefore gave rise neither to allergic sensitiza-
tion nor to the formation of circulating antibodies in the animals tested. The agent, which is produced by acid extraction of Brucella organisms and subsequent precipitation at pH 4.5, has become known under the name PEBA (purified extract of Brucella abortus).

Bovine brucellosis is now non-existent in Denmark. Also porcine brucellosis has been the subject of intense studies. When this disease first appeared in this country in 1935, a very thorough description was given of its clinical and pathological aspects, and the causative organism (Bruc. suis Thomsen) was submitted to careful examination, which showed it to differ slightly from the porcine Brucella type (Bruc. suis Traum) previously isolated in the U.S.A.

Brucellosis has never been a stationary disease among swine in Denmark, but sporadic outbreaks have continued to occur at longer or shorter intervals. Until the beginning of the fifties, when it was discovered that infection with Bruc. suis Thomsen was enzootic among hares in certain areas, it was quite an enigma from what source of infection these outbreaks originated. Also this discovery was made by workers at the Serum Laboratory.

Tuberculosis

Through a long period tuberculosis was the subject of very intense research at the institute. Thus, in the years up to 1915, substantial contributions were made to the elucidation of the part played by the avian type of tubercle bacteria in tuberculosis of swine, and in the early twenties it was discovered that avian tubercle bacteria was a not uncommon cause of endometritis and abortion in cattle. Later studies (in the forties) revealed that avian tuberculosis infection in cattle might give rise to peritoneal lesions, and occasionally also to ulcerative lesions of the intestine and to infiltrative lesions of the udder and kidney.

Through the twenties and thirties large-scale research was carried out on tuberculina as a diagnostic aid in tuberculosis of cattle.

This research was occasioned by the fact that the intradermal tuberculin test, which had at that time superseded the thermal test, was falling into discredit because of a high percentage of no-lesion reactors.

It was shown that no-specific reactions to bovine tuberculin could be explained as a result of sensitization by other mycobacteria, notably avian and human type tubercle bacteria and paratubercle bacteria, and that by simultaneous intradermal testing with bovine and avian tuberculin it was in most cases possible to decide, on a herd basis, whether bovine tuberculosis was present or not.

The testing procedure worked out on the basis of these results has been universally adopted, in a more or less modified form, under the name of the intradermal comparative tuberculin test. The Serum Laboratory has also been concerned with problems regarding the differential diagnosis of tuberculosis at autopsy. Especially the lesions caused by Cb. equi in the sub-maxillary lymph nodes of swine was given much attention, because they involved a commercially very important meat-inspection problem.

Bovine tuberculosis has by now been reduced to a negligible level in Denmark.

Paratuberculosis (Johnes's disease)

Much effort has been devoted to improving the reliability of the complement-fixation test in paratuberculosis. One step forward was made when antigens were produced by means of which it proved possible to differentiate between, on the one hand, CF reactions caused by bovine tuberculosis infections, and, on the other hand, CF reactions caused by paratuberculosis or by bovine or human type tuberculosis. The method of producing these antigens is based on extraction of organisms in an alkaline solution.

The work on paratuberculosis led to the incidental discovery that this infection may also affect swine, giving rise to caseous lesions of the mesenteric lymph nodes.

Mastitis

Bovine mastitis has been — and is — a major concern of the institute, and much of the research underlying the present mastitis control scheme has been done here.
Numerous papers have been published on the aetiology, diagnosis, treatment, and prophylaxis of mastitis. Until about the middle of the fifties attention was mainly focussed on the more or less specific bacterial infections of the udder, while after that time it has gradually been recognized that great importance should also be attached to so-called occupational mastitis, i.e., mastitis arising as a result of poor management (e.g., faulty milking technique, bad hygiene, nutritional deficiencies) paving the way for infection with potential pathogens.

Botulism

Through experimental investigations carried out in the fifties, two previously recognized disease entities, viz., infectious equine paraplegia and enzootic bovine bulbous paralysis, were shown to be manifestations of botulism (type C).

Andrology

Partly in cooperation with other institutes, important studies have been made on malformations and other disorders of the bovine male genital organs, and on the ultrastructure of the bull sperm.

These studies have led to the discovery of hitherto unknown malformations of the genital tract of the bull (e.g., segmental aplasia of the Wolffian duct) and of the bull sperm, and added much to our knowledge of genital infectious disorders as the cause of infertility in bulls. Recently it was demonstrated that seminal vesiculitis may be produced by infection with Mycoplasma.

Diseases of fur-bearing animals

The Danish Veterinary Serum Laboratory was among the first in the world to take up research on diseases of animals kept for production of furs.

Major contributions have been made in the fields of mink distemper and virus enteritis, especially as regards epidemiology and specific prophylaxis, and a septic pneumonia in mink caused by *Pseudomonas aeruginosa* was first described from this institute.

Furthermore, the institute participated in a team-work that, in all essentials, unveiled the aetiology of the disease in mink known as "yellow fat".

Diseases of wild-life

Studies on diseases of wild-life have been carried on since the middle of the thirties. Numerous papers have been published on a variety of diseases in different species of animal.

It was through these studies it was discovered that hares were the principal reservoir of porcine brucellosis.

Diseases of fish

Infectious diseases of trout have been studied at the Serum Laboratory since the beginning of the sixties. At an early stage of these studies the first isolation in the world was made of the virus causing haemorrhagic septicemia (Eggert disease) of rainbow trout.

Current Research Projects

It is hardly possible, in an institute like the Danish State Veterinary Serum Laboratory, to make a clear distinction between specific research projects and research incidental to routine diagnostic work. In fact, even specific projects will in most cases have emanated from the routine.

In the following, brief mention is made of the more important specific projects.

*E. coli* infections in calves

Studies are going on concerning the pathogenicity of various O-groups of *E. coli* for colostrum-deprived and colostrum-fed new-born calves, and on the protective effect of specific antiserums.

Also the protection afforded to calves through vaccination of the dams against *E. coli* with a vaccine containing Freund's adjuvant is subject to experimental investigation.
The possibility of hypo-gammaglobulinaemia being a decisive factor in the pathogenesis of coli septicaemia is being studied under field conditions.

**Cl. perfringens infections in pigs**

The necrotizing enteritis in piglets caused by *Cl. perfringens* type C, is subject to intensive studies with regard to clinical and pathological features, pathogenesis, epizootiology and prophylaxis.

**Mastitis**

The role of staphylococci as a cause of bovine mastitis has been thoroughly studied through a number of years. Efforts are now centred on phage-typing of strains, with a view to elucidating not only the epizootiology of bovine staphylococcal infections, but also their possible zoonosis aspects.

The problem of contributing causes to mastitis (e.g., machine milking, housing conditions, feeding, hygiene) is subject to investigation on a large scale.

Physiological variations in the milk cell count are being studied, and efforts are made to improve both the direct and the indirect methods of determining the cell content.

**Leukosis**

Experiments concerning the pathogenesis of enzootic bovine leukosis are running. Also the epizootiology of this disease is being studied.

**Aujeszky's disease**

The epidemiology of Aujeszky's disease, and the spread of the virus of this disease among pigs in Denmark, are being studied through serological surveys and virus isolations. The ways of transmission of the disease are being studied experimentally. Experiments with prophylactic treatment of piglets with antisera are planned.

**Swine erysipelas**

The possible effect of vaccination against swine erysipelas on the incidence of arthritis in pigs is being examined in a field experiment.

**Diseases of fish**

Efforts are being made to work out a technique for serological identification of the virus of Egtved disease, or viral haemorrhagic septicaemia of rainbow trout, and studies on the ways of transmission of infectious necrotizing pancreatitis of trout are planned.

**Immunofluorescence**

A special unit has been established for production of fluorescence-marked antibodies, and for adaptation of immunofluorescence techniques to new fields of veterinary research and diagnosis.

**Nitrite poisoning**

When it had been shown that high concentrations of nitrite could be found in drippings from ventilation shafts, and deaths resulting from the intake of such drippings had occurred among animals (especially pigs), the question arose whether this nitrite was formed as the result of a simple chemical reaction or through microbial activity. This question is subject to research at the Serum Laboratory. Preliminary results seem to indicate that the formation of nitrite is brought about by organisms of the genus *Nitrosonomas*.

**Andrology**

Studies are continuing on congenital malformations of the reproductive organs of the bull, and on the ultrastructure of normal and pathological sperms.

**Health and environment**

A project has been launched for study of the relation of animal health to environmental and nutritional conditions. It includes some 40 herds of cattle and swine, in which exact records are
kept of, on the one hand, cases of death or disease, and, on the other hand, feeding and performance. In addition, examinations are made of housing conditions, indoor climate, general hygiene, and management.

**Service Functions**

**Diagnosis**

As mentioned in the introduction, the Serum Laboratory carries out diagnostic examinations relative to scheduled animal diseases, and offers a general diagnostic service to veterinary practitioners.

The diagnostic service includes ordinary post-mortem examinations, bacteriological, virological, and parasitological examinations, histopathological examinations, serological and haematological examinations, biochemical analyses.

The examination of post-mortem material is perhaps the most important part of the diagnostic work; 10,000—12,000 specimens are examined annually, the majority from calves, pigs, and fur-bearing animals. Practically all specimens are examined bacteriologically. Virological examination was carried out in ab. 2,000 cases in 1966.

Parasitological examinations of faeces or post-mortem material is carried out in some 5,000 cases a year.

A great deal of the routine work consists in sero-diagnostic examinations of blood (chiefly for fowl typhoid, other salmonelloses in poultry, paratuberculosis, brucellosis) and milk (for brucellosis). A total of 250—300,000 blood samples and a similar number of milk samples are examined yearly. Some 50 per cent of the milk samples are also examined for possible residues of antibiotics.

The control of enzootic bovine leukosis involves a great number of haematological examinations. In 1966, some 50,000 such examinations were made. A ten-fold increase of this number is expected, however, after a scheme for systematic eradication of bovine leukosis has been launched. Only by the use of electronic counters will it be possible to carry through this work.

Mastitis is probably the most labour-consuming field of work at the institute, involving 8—400,000 bacteriological examinations and 100—150,000 cell counts a year, plus a good deal of field work.

**Supply of biological products**

The institute is producing antisera for *E. coli*, *Diplococcus pneumoniae*, *Erysipelothrix rhusiopathiae*, *Salm. dublin*, and *Paste. multocida*, and vaccines for mink distemper, swine erysipelas, pasteurellosis, and leptospirosis. In addition, bovine and avian tuberculins are produced.

Certain products are purchased from other Danish or foreign institutes, f. inst. tetanus vaccine and antiserum, foot and mouth disease vaccine and antiserum, and vaccines for rabies, botulism, mink enteritis, anthrax, and blackleg.
List of communications (1958—1968)\(^1\)

from

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\(^1\) For papers published up to 1958, reference is made to publication No. 338.
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