INTRODUCTION

The Onderstepoort Veterinary Institute (OVI), as it is currently known, is internationally renowned for its pioneering research on diseases of livestock and other animals. It is therefore timely that the most notable of these achievements, which have been published in appropriate scientific periodicals/journals over the years, be concentrated into a single article for more general information and easy reference purposes. In this article OVI’s research highlights are presented chronologically starting with the earliest contributions made by its founder, Sir Arnold Theiler, before the Onderstepoort Institute was established. Then the most important achievements are briefly described as they materialised under the various heads of the Institute, mostly having the title of Director. In the case of some directors who were in office for very brief periods, the research achievements are either dealt with collectively or merged into the foregoing and following periods.

PRELUDE

Systematic veterinary research in southern Africa had its origin in the worst outbreak of animal disease this country has ever experienced, i.e., the rinderpest (RP) pandemic that entered what is now South Africa in 1896. The Cape Colony had reacted by eliciting the assistance of the world famous Robert Koch whereas the Zuid-Afrikaansche Republiek (later the Transvaal province) appointed the dynamic young Swiss veterinarian, Arnold Theiler, who had been in the country since 1891, as ‘Gouvernements-veearts’ (state veterinarian) on 11 May 1896 with the specific task to combat RP. Theiler established a field laboratory in the Marico district in 1896 where he and H. Watkins-Pitchford, who had been appointed Principal Veterinary Officer in Natal in 1896, in an amazingly short period of six weeks developed the essentials of what proved to be the first really effective immunisation process against RP, a serum-virus type of vaccine (Figure 1).

Theiler then moved to the farm Waterval, north of Pretoria, where, at a laboratory established at Eberhard’s Hotel, most of his further work on the improvement of the new vaccine was finalised in cooperation with two imported French scientists, J. Danysz and J. Bordet. In July 1898 Theiler founded his first permanent laboratory at Daspoort, previously a ‘disinfection station’ commissioned by him in 1897 for disinfection of animal products such as hides and skins possibly contaminated with RP that had subsequently been abandoned (Gutsche, 1979). He called this laboratory a vaccine institute, which apart from RP vaccine also produced vaccines against...
blackquarter, lungsickness of cattle and smallpox of humans (Vogel & Heyne, 1996).

Owing to the efforts of mainly Theiler and Koch [who developed a rather unsafe, but widely used, ‘vaccine’ from the bile of infected cattle (*Bos taurus/indicus*)] the RP epidemic had been practically brought under control by 1898 – only sporadic cases occurring during the Anglo-Boer War – but only after destroying almost half of the cattle population (Figure 2) and many of the big game species, such as buffaloes (*Syncerus cafer*), in the four countries that later became South Africa.

Theiler’s enlistment at the outbreak of the war was followed by a short spell as a ‘horse doctor’ in the State artillery with the Boer forces, whereafter he returned to his laboratory at Daspoort. F.B. Smith, Director of the Transvaal Department of Agriculture of the post-war Transvaal government, appointed Theiler as Government Veterinary Bacteriologist in 1903 (Gutsche, 1979). His activities included continued production of small pox and lungsickness vaccines as well as research on African horsesickness (AHS) (Gutsche, 1979).

Another catastrophic cattle disease hit the country in 1902 when East Coast fever (ECF) was introduced by cattle imported from East Africa. The latter action was part of the Milner (now Governor of the Transvaal Crown Colony) government’s policy of importing ‘repatriation’ cattle from other countries to replace those decimated by the British scorched-earth war policy and the ravages of RP. ECF required intensive research because its cause and mode of transmission were unknown. It was Theiler who proved conclusively that ‘Rhodesian redwater’, as this new disease was initially called, was not a form of redwater but a completely new disease, thereby resolving the mystery of its aetiology (Gutsche, 1979). Lounsbury (1904) helped Theiler in 1903 (Gutsche, 1979) to prove that the disease was tick-borne, its vector shown to be the three-host tick, *Rhipicephalus appendiculatus*, and the protozoan parasite responsible was named *Theileria parva* in his honour.

**ESTABLISHMENT OF THE NEW LABORATORY AT ONDERSTEPOORT**

Theiler was never happy with his Daspoort facility and the laboratory became too small for the growing demand for vaccine production and research. Not only was it unsuitable for research but it was also unhygienic and therefore posed risks for human health. In fact, Theiler lost several of his assistants from typhoid fever.

In 1906 Theiler inspected a portion of the farm De Onderstepoort and regarded it as a much more suitable proposition than Daspoort. The grazing was good, the land arable and it was furthermore said to be notorious for African horsesickness (AHS) (Coetzer & Guthrie, 2004). Theiler canvassed F.B. Smith, the Director of Agriculture, who requested Adam Jameson (Commissioner of Lands in the government) to obtain approval from the Executive Council for the proposed project.

Funds (£60 000) were duly voted for the laboratory and 500 acres of the farm De Onderstepoort was eventually acquired. Theiler could begin planning his new Institute. ‘Responsible government’ for the Transvaal was only instituted after the election early in 1907 and Theiler’s first official meeting with the politicians who would be so important in his future career occurred on 9 March 1907 when Generals Louis Botha, J.C. Smuts and others visited him at Daspoort (Gutsche, 1979). Louis Botha, who became Prime Minister and Minister of Agriculture of the Transvaal when ‘responsible government’ was instituted in 1907, was also a farmer and Theiler and Botha came to know each other quite well, a relationship used productively by both, but sometimes also exploited by Theiler (Gutsche, 1979).

Patrick Eagle, Chief Architect of the Public Works Department, was responsible for drawing up the plans for the Institute, Theiler supplying him with the information he had acquired in Europe on the best design for a bacteriological institute. His comprehensive plans included not only labora-
many laboratories as well as necropsy and services facilities. The massive main building began in June 1907. It would house farm services, staff quarters and transport. Work on the laboratory buildings but also stabling for a variety of animal species, Canis familiaris kennels, a bit further away stood the dog (Canis familiaris), piggery, small animal facilities and an isolation stable. There were supposed to have been opened by him. However, he was attending the National Convention in Durban! Jakob de Villiers, the Attorney General and acting Prime Minister, therefore conducted the opening of the Conference in the Executive Council Chamber in the Government Building in Pretoria. Theiler took as many of the delegates to the Conference as he could to see his Institute and they duly signed his visitor’s book, but Onderstepoort, which had cost the then stunning amount of £80 000, was never officially inaugurated (Gutsche, 1979).


Research that had been conducted independently by M’Fadyean, Theiler and Nocard in the early 1900s had shown that AHS was caused by a filterable virus. The pioneering research conducted by Theiler suggested the presence of immunologically heterologous strains of the AHS virus (AHSV) in the natural environment. In practice this meant that horses that had acquired immunity against one strain of virus were not necessarily protected against infection with another.

The discovery of the unique microbiological organism that causes bovine anaplasmosis, a disease also known as gallsickness or galsiekte, in 1908 (first published in 1909) was another one of Theiler’s many achievements. Smith and Kilbourne in the USA had seen the peculiar ‘marginal points’ in 1893 but they regarded them as stages in the life cycle of Babesia bigemina. Theiler decided that the marginal points in the erythrocytes were protozoan parasites devoid of cytoplasm and named the organism Anaplasma marginale. Only when the transmission electron microscope became available many decades later was the rickettsial nature of these coccus-like bodies revealed. Early in 1910 (published in 1912) Theiler also discovered Anaplasma centrale (he named it A. marginale var. centrale in 1912), which was considerably less pathogenic and conveyed partial protection to infection with the much more virulent A. marginale. The original source proved to be serotype 4 of BT virus (BTV). A plurality of strains, as in the case of AHSV, was suspected even in those early days. Despite shortcomings, this vaccine gave fairly satisfactory control and was used in the field for almost 40 years before it was replaced with more sophisticated products (see later) (Verwoerd & Erasmus, 2004).

The earliest reasonably successful vaccine developed by Theiler consisted of the simultaneous inoculation with virus and polyvalent immune serum, the so-called serum-virus method of immunisation (Coetzer & Guthrie, 2004), a technique that he and Watkins-Pitchford had previously used for RP. Theiler also demonstrated the filterability of the aetiological agent of bluetongue (BT), and thus its viral nature, in the early 1900s. He developed a BT ‘vaccine’ consisting of infected sheep (Ovis aries) blood containing a relatively innocuous strain of what later proved to be serotype 4 of BT virus (BTV). A plurality of strains, as in the case of AHSV, was suspected even in those early days. Despite shortcomings, this vaccine gave fairly satisfactory control and was used in the field for almost 40 years before it was replaced with more sophisticated products (see later) (Verwoerd & Erasmus, 2004).

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of his *A. centrale* strain was blood from cattle obtained from the Karoo. Blood from cattle infected with *A. centrale* has been used as a very effective vaccine against anaplasmosis ever since, not only in South Africa but in other countries such as Australia, Israel and South America, who have been provided with the Theiler isolate (Potgieter & Stoltsz, 2004).

Following the example of Hutcheon, Robertson and others, Theiler developed a redwater vaccine, which he *inter alia* tested in imported English cattle. It consisted of blood obtained from carrier–donor cattle infected with *Babesia bigemina* (Knuth & DuToit, 1921). The vaccine was apparently routinely prepared from 1912 and possibly issued as a separate product initially but soon combined with anaplasmosis, making use of donor cattle with a mixed infection of the two parasites, and was sold for a shilling a dose (Potgieter & Stoltsz. 1944).

One of the greatest research achievements of the early 20th century was the final elucidation of the true nature of lamsiekte, or bovine botulism, a disease that had caused havoc among cattle in South Africa over very many decades and which occurs in many other countries. Lamsiekte had received attention by several veterinarians from as early as the late 19th century. Duncan Hutcheon (Figure 5) was first to ponder on the cause of the disease in the Cape of Good Hope. He satisfied himself that both ‘lamsiekte’, as it was then called, and ‘stijfziekte’ (stiffness) were due to defective nutrition caused by a shortage of phosphates, advising farmers to feed bone meal prophylactically to their cattle. Thus, Hutcheon had determined the likely cause by careful observation – even noticing the presence of pica (a depraved appetite, including an excessive craving for bones) in cattle that developed the disease on devouring such material – and astute reasoning, and probably also by listening carefully to observant farmers, long before Theiler and his colleagues finally solved the entire problem (Gutsche, 1979; Kriek & Odendaal, 2004).

The McKee brothers had offered the farm Armoedsvlakte close to Vryburg, which was uninhabitable for cattle on account of the occurrence of lamsiekte, to Theiler free of rent for research purposes. P.R. Viljoen, the second South African to qualify as a veterinarian (the first was J.F. Soga), who had been posted on this farm in 1914 to conduct research on the disease, succeeded in confirming the work done previously by Mitchell and Walker (both in 1913) (Kriek & Odendaal, 2004) and repeatedly reiterated by stock farmers, i.e., he reproduced lamsiekte by feeding rotten carcass material to cattle, thus proving that it caused the disease. However, as could be concluded later when the entire sequence of events had been sorted out, there had been no phosphorus deficiency in the grazing on Armoedsvlakte at the time that Viljoen had made his observations, pica being at its highest level with the virtual absence or dryness of grass in winter and lowest in spring with its luxuriant young grass. He could therefore not explain why cattle would ingest carcass material spontaneously in the veld under natural conditions (Gutsche, 1979). Parts of the riddle therefore remained unsolved.

Theiler, who had prematurely retired at the beginning of 1918 – R.E. Montgomery took over from 1918–1920, but then left for East Africa – to devote himself mainly to family matters, was asked by H.C. van Heerden, the Minister of Agriculture, to re-enter government service to concentrate entirely on lamsiekte research at Armoedsvlakte. Theiler acceded on condition that he was to have complete freedom from administrative duties and be answerable to no one. He was also to have sufficient staff and funds for experimental animals and their keep, which was granted. On 24 February 1919 Sir Arnold (he had been elevated to Knight Commander of the Order of St Michael and St George in 1914) and Lady Theiler arrived at Armoedsvlakte, which he regarded as situated in the best farming country in the world for cattle, and settled into the rudimentary government constructed house. This time Theiler had sufficient time at his disposal to wander with the cattle and closely observe their grazing habits – ‘an expert become cattle-herd’.

Whereas there had been no phosphorus deficiency in the grazing at Armoedsvlakte at the time that Viljoen had conducted his research, pica was very evident when Theiler had made his field observations. Theiler, assisted by Theo Meyer, promptly dosed cows ravenous for rotten bones (i.e., showing pica symptoms) with carcass material. The animals contracted typical lamsiekte in 4–10 days. He had conducted the experiments that provided him with the solution in less than a week after his arrival on the farm. It was shown experimentally by Theiler and his colleagues Green and Du Toit that lamsiekte could be effectively prevented from occurring by systematic dosing of cattle with bone meal (Figure 6) (Gutsche, 1979; Henning, 1956). The aetiological chain of events which lead to disease was completed when Robinson (1930) identified the toxin-producing bacterium, *Clostridium botulinum* type D, and in 1938 Mason and collaborators were first to develop a formol-toxoid vaccine against lamsiekte, now also known as botulism (Kriek & Odendaal, 2004).

Theiler was re-appointed on 1 April 1920, this time as Director of Veterinary Education and Research as a sequel to being offered – by Genl J.C. Smuts in 1919 – the joint appointment as Dean of the – to be established – Faculty of Veterinary Science and Director of Veterinary Research. Much of Theiler’s time and that of his scientific staff in the early 1920s was taken up by the establishment of the Faculty of Veterinary Science in 1920 as a subsidiary function of the...
Institute, virtually all the teaching from the 2nd year of the course onwards being conducted by researchers on a part time basis. The first veterinary surgeons graduated from the Faculty in 1924 (Figure 7).

Heartwater has been known for many centuries in what is now South Africa. The Voortrekker pioneer, Louis Trichardt, probably provided the first written record of heartwater in his diary in 1838 when his sheep succumbed to a disease known locally as ‘nintas’ three weeks after severe tick infestation while trekking through an area which is now in the Limpopo Province. Since it was shown independently in 1898 by Dixon and Edington that heartwater could be transmitted by sub-inoculation of blood from symptomatic to susceptible animals, it was concluded that heartwater was probably caused by a sub-microscopic virus. In 1900 Lounsbury confirmed the long-standing assumption that the bont tick, *Amblyomma hebraeum*, transmitted the disease. It was an American rickettsiologist, Cowdry, from the Rockefeller Institute, who was invited by Theiler to Onderstepoort to determine whether heartwater was possibly a rickettsial disease, who first demonstrated the causative rickettsial micro-organism microscopically in 1925 (Allsopp et al., 2004).

**RESEARCH FROM 1927–1948 WHEN DR. P.J. DU TOIT (FRSSAf) WAS DIRECTOR OF VETERINARY SERVICES**

Du Toit (Figure 8) had trained in both zoology and veterinary science and was, for all practical purposes, in control of Onderstepoort from his arrival in December 1919 when Montgomery had decamped to East Africa. He was, moreover, appointed Acting Director of Veterinary Education and Research when Theiler left for a 6-months ‘sabbatical’ to mainly Switzerland in 1921 and administered the Institute to a large extent for the next few years while Theiler concentrated on the education of the new veterinary students and the activities of the outstations, such as Armoedsvlakte. Du Toit was also much more the manager of than the participator in the various research programmes and believed in delegating the research responsibilities to the scientists concerned. This resulted in the development of discipline-based research sections (D.W. Verwoerd, unpubl. data, 2006).

Rimington was a biochemist from the United Kingdom who was appointed at Onderstepoort specifically to study ‘geeldikkop’ (tribulosis) in sheep, suspected since Theiler’s time to be associated with a plant known as the dubbeltjie (*Tribulis terrestris*), after another serious outbreak had occurred in the Karoo in 1926/27. Rimington and Quin identified phylloerythrin, a photodynamic porphyrin, as the cause of the disease, later, however, shown to be only part of the pathogenesis (see later). He also isolated the toxic principles (*icterogenins*) from *Lippia rehmanni*, another plant causing icterus, and studied congenital porphyria in cattle.

Monofluoroacetate, the toxic principle of the plant known as gifblaar (*Dichapetalum cymosum*), was first isolated by Marais in 1943 (Kellerman et al., 1988). It is now known that monofluoroacetate blocks cellular respiration via the Krebs cycle, which was poorly understood at the time. Marais’s discovery therefore made a significant contribution to unraveling the cycle.

Trypanosomosis, also known as ‘nagana’, has been known as a fatal disease of cattle by some of the inhabitants of Africa for many centuries. Outbreaks of this tsetse fly-borne disease reached epidemic proportions in Zululand (now part of KwaZulu-Natal) in the early 20th century and since there was no other method of control, and wild animals were clearly the source of infection for farm animals, several shooting campaigns were conducted in an attempt to control the disease.

Harris was appointed in 1921 to study the bionomics of the vector tsetse flies. On the basis of his studies he developed the well-known Harris flytrap that caught millions of tsetse flies, and it was thought at one stage that it would be possible to eliminate the tsetse and control the disease in this way. As it subsequently became clear that Harris trap catches went up and down according to fluctuations in tsetse populations, it was eventually concluded in the early 1940s that the trap was
little more than a surveying tool (Du Toit, 1954).

In 1928 Viljoen, who featured so prominently in the previously mentioned lambsiekte research but was given so little credit for it by Theiler, developed an attenuated spore vaccine against anthrax for use in animals. This was more effective than the spore vaccine introduced in 1920 produced after the method of Cienskowsky, but was replaced by the highly effective Sterne spore vaccine in 1937. It consists of a toxigenic, virtually avirulent, non-capsulating strain of *Bacillus anthracis* isolated by Sterne. It is essentially still used as originally formulated, i.e., a suspension of $\pm 10^7$ spores per millilitre in 1.5% glycerol-saline to which saponin has been added which, together with the glycerine, enhance the immunogenic effect. Although this live vaccine essentially consists of a wild strain of *B. anthracis*, it is non-pathogenic for most domestic and wild animals and is still the vaccine of choice today virtually worldwide, 70 years after its discovery (De Vos & Turnbull, 2004).

Effective vaccination against AHS eluded researchers for many decades. Theiler’s serum-virus method of vaccination and his discovery of the plurality of AHSV strains have been described previously. The first really promising advance in research on AHS was made by Alexander (Figure 9) in 1933 when he proved that the normally viscerotropic strains of AHSV not only became neurotropic when serially passaged intracerebrally in adult mice (*Mus musculus*) – using the technique pioneered by Max Theiler (son of Arnold Theiler) in the USA for yellow fever virus – but also became less virulent for horses (attenuated) without losing their immunogenicity. Alexander followed this up in 1938 by culturing the virus in the chicken embryo by inoculation of the chorio-allantoic membrane and found that passage in chicken embryos (avianisation) also leads to attenuation of the virus. Attenuated mouse strains were used from 1936 to prepare a highly effective polyvalent neurotropic vaccine (Coetzer & Guthrie, 2004). Erasmus developed the currently used method of selection of large plaques of the virus in 1974 (see later).

AHS is a disease of the summer months and it was observed from shortly after the much-feared ‘paardeziekte’ was first recognised in South Africa that outbreaks were arrested by frost. As early as 1903 Pitchford and Theiler suggested that biting insects transmitted it. They moreover showed that horses could be protected from AHS if they were housed in mosquito-proof stables. R. du Toit, after a series of unsuccessful trials with mosquitoes in 1943, turned his attention to *Culicoides*, the midge that is so plentiful in South Africa. By feeding field-collected *Culicoides* – probably *C. imicola* – on BTV-infected sheep he transmitted BT to susceptible sheep. He is reported to have transmitted AHS by *Culicoides* bite in the same way. Thus the vexing riddle of the mode of transmission of these two very important arthropod-borne viruses was finally elucidated (Meiswinkel et al., 2004).

In 1940 Neitz (Figure 10) discovered the first chemotherapeutic cure for heartwater of ruminants in the form of Uleron, one of the first sulphonamides to be developed (in Germany). At the time there was no cure or prophylaxis for this important disease of cattle and other ruminants. It was the first use of this drug against rickettsial infections of animals and humans. The next year Neitz developed a vaccine against heartwater consisting of infected sheep blood that could be administered with relative safety to very young calves. This was soon followed by the development of an infection and cure – initially Uleron was used which was later replaced by the tetracycline antibiotics (Weiss) – method of immunisation against heartwater for older cattle and other domestic ruminants (Allsopp et al., 2004).

R. du Toit (Figure 11) was also the brain behind the successful eradication of the most important South African tsetse fly vector of nagana, *Glossina palpalipes*. Having first evaluated the efficacy of DDT and BHC (*benzene hexachloride*) in controlled studies, Du Toit and Kluge initiated an aerial spraying campaign (assisted by the South African Air Force) in Zululand in which tsetse-infested areas were sprayed with DDT, first as atomised liquid droplets in 1945 and subsequently as a thermal aerosol (Figure 12). Applied thus, DDT and BHC have no residual action. In 1949 Kluge started
identifying the breeding sites of the tsetse flies by searching for their pupal casings in the sand of riverbeds and valleys of Zululand (Pringle, 1982). Subsequent aerial spraying with DDT and BHC could therefore be aimed specifically at the breeding areas. Thermal smoke generators were used to apply the insecticides in deep valleys where aerial spraying was impractical. The successful campaign, in which G. pallidipes was exterminated, was completed in 1952 (Du Toit, 1954). G. brevipalpis and G. austeni, however, persisted but only caused sporadic cases of nagana until about 1990 when a widespread outbreak occurred which had to be contained by chemotherapy and other measures (Connor & Van den Bossche, 2004).

Mason, Coles and Alexander made the first breakthrough towards the development of a really effective vaccine against BT in 1939 by cultivating the virus in embryonated eggs. Alexander further developed the technique in 1947 by inoculation of virus strains via the yolk sac and intravascular routes. This was followed in 1948 by the demonstration by Neitz, by means of cross-protection studies conducted in sheep, of the plurality of BTV immunogenically distinct serotypes thereby explaining the problem of vaccine failures and the importance of having a polyvalent vaccine. BTV was also adapted to the brains of suckling mice by Van den Ende, Linder and Kashula in 1954, but no attenuation was found. Serial passage of the various virus strains in eggs led to their attenuation for sheep and an effective BT vaccine could be prepared by this technique and later by growth of BTV in cell culture (see later) (Verwoerd & Erasmus, 2004). In 1948 Haig developed an excellent avianised vaccine against canine distemper, by propagating the virus on the chorio-allantoic membrane, which was used worldwide for many decades (Henning, 1956).

One of the most useful and highly rated scientific textbooks ever produced by an Onderstepoort researcher was Mönnig’s (Figure 13) pioneering classic, Veterinary Helminthology and Entomology in 1934. It would remain the standard, especially for tuition of veterinary students, for decades and was later adapted and updated by E.J.L. Soulsby under the title Helminths, Arthropods and Protozoa of Domesticated Animals.

G. van de Wall De Kock (1948 – 1949) and J.I. Quin (1949 – 1950) were Directors of the Institute – both had the title of Director of Veterinary Services – for such short periods that the research activities that occurred during their regimes can conveniently be merged into the foregoing and following
periods. De Kock served for only one year (1948–1949) before reaching retiring age and Quin, who was appointed in 1949, died unexpectedly from a heart attack early in 1950.

RESEARCH FROM 1950–1961 WHEN DR R.A. ALEXANDER WAS DIRECTOR OF VETERINARY SERVICES

Quin was the first Director of Onderstepoort who had qualified at the new Faculty and Alexander the second. They were members of the Classes of 1924 and 1925, respectively. Both were outstanding researchers making significant contributions in the toxicological (Quin) and virological (Alexander) disciplines. Alexander was the last head of the Institute to bear the title of Director of Veterinary Services for the entire period of his reign.

Although what is now regarded as the classic form of East Coast fever – a cattle-adapted variant of T. parva – had been eradicated from South Africa by 1955, a variant form of the disease, named Corridor disease because the first recognised outbreak occurred in the so-called corridor of land between the Hluhluwe and Umfolozi Game Reserves in Natal – now KwaZulu-Natal – was discovered by Neitz in 1953. An outbreak of Corridor disease, also known as buffalo disease, can be halted in its tracks by the removal of cattle from contact with African buffaloes (Syncerus cafer) (Figure 14). This was relatively simple in those early days of the disease when infected buffaloes only occurred in national and provincial game reserves. It has, however, become much more difficult in recent years because of the unprecedented development of game ranching and the relaxation, due to pressure by organised agriculture, of the previous stringent regulations limiting the transportation and spread of buffaloes from endemic areas (see later) (Lawrence et al., 2004).

Neitz also discovered, in 1954, that sweating sickness of young cattle, a disease which had been known for many years in South Africa and some other African countries, was transmitted/caused by the bont-legged tick, *Hyalomma truncatum*. Only female ticks caused disease and he found it possible to grade the severity of the disease by progressive removal of the ticks during the ‘incubation period’. From this Neitz deduced that the ticks produced a toxin that was responsible for the disease. The aetiological agent of sweating sickness, however, remains unclear because of the presence of an incubation period and the development of a solid immunity in recovered animals from which it is possible to produce immune sera for curing affected animals if used early in the course of the disease (Oberem et al., 1985).

First to use the newly implemented cell culture technology for the cultivation of viruses at Onderstepoort was Haig (Figure 15) who cultured BTV and developed a quantitative neutralisation technique for BT in 1956. This enabled Howell (Figure 16) to identify 12 BTV serotypes in 1960. McIntosh paved the way in AHS by using the technique to identify seven AHSV serotypes in 1958. In subsequent years this led to great improvement of the vaccines against BT and AHS (see later) (Verwoerd & Erasmus, 2004).

Pols made the first significant breakthrough in research on besnoitiosis (elephant skin disease or ‘olifantswelsiekte’) of cattle – a disease with a relatively wide geographic distribution – in 1954 when he succeeded in transmitting the disease to cattle and rabbits (*Oryctolagus cuniculus*) by sub-inoculation of blood from an acutely affected natural bovine case. The rabbit proved to be an excellent model for further research on the disease (see later) (Bigalke & Prozesky, 2004).

Lumpy skin disease was first diagnosed in South Africa in 1954 when the Institute’s Director, Dr R.A. Alexander, asked a farmer to send over a biopsy of a diseased animal. The disease was caused by a bovine virus that was transmitted by the bont-legged tick, *Hyalomma truncatum*. A clear cell culture system was found in 1955; in 1956, P.G. Howell developed a quantitative neutralisation test for BTV; and in 1956, D. Haig used elegant tissue culture techniques to do the first serotyping of BTV virus strains. The first specific vaccine against lumpy skin disease was developed by Dr K.E. Weiss in 1958 and was the eighth Director of Onderstepoort.

**Figure 14.** African buffaloes, the carriers of diseases such as Corridor disease and foot-and-mouth disease.

**Figure 15.** D. Haig and co-workers developed a quantitative neutralisation test for bluetongue in 1956.

**Figure 16.** P.G. Howell used elegant tissue culture techniques to do the first serotyping of bluetongue virus strains in 1960.

**Figure 17.** K.E. Weiss developed the first specific vaccine against lumpy skin disease and was the eighth Director of Onderstepoort.
in 1944, having been encountered for the very first time in 1929 in what is now Zambia where it was called pseudo-urticaria. In South Africa it spread rapidly through the entire country, causing considerable economic losses to the cattle industry.

The so-called Neethling strain of the virus was isolated in cell culture by Alexander et al. in 1957 and attenuated by 20 serial passages on the chorio-allantoic membranes of embryonated eggs by Weiss (Figure 17) and his research team in 1959.

Currently the virus used for vaccine production is grown in cell culture (Coetzer, 2004). Van Drimmelen introduced vaccination with the Rev. 1 mutant strain of Brucella melitensis, which has been highly effective for the control of B. ovis infection in sheep, in South Africa in the late 1950s.


Jansen (Figure 18), who had been awarded the prestigious Theiler medal when he qualified from the Onderstepoort Faculty in 1944, was devoted to research. Although he eventually occupied one of the most senior administrative positions in the Department of Agriculture, he managed to keep on doing research. After retirement his activities as researcher, combined with teaching sheep diseases at the Faculty, were continued with absolute dedication until he died, virtually ‘at the laboratory bench’, in 1987. Both Alexander and Weiss were involved in research at Onderstepoort on the development of suitable vaccines against Rift Valley fever (RVF) in ruminants. Basically the strain of virus used for the production of live vaccine is the attenuated, suckling mouse, neuro-adapted Smithburn strain. It was subjected to further passages in mice and embryonated eggs before being used for the production of a freeze-dried mouse brain vaccine. Later it was propagated in cell culture. This vaccine, which conveys a life-long immunity, is used mainly in young sheep before they are mated as it causes abortions and foetal abnormalities in pregnant ewes, i.e., is teratogenic. Onderstepoort therefore also developed a formalin-inactivated vaccine produced from wild RVF virus for use in pregnant sheep and cattle. The immunity the latter induces is, however, of short duration (Swanepoel & Coetzer, 2004).

Basson (Figure 19) was employed as regional state veterinarian in South West Africa (now Namibia) when he discovered the causal agent of ‘uitpeuloog’ (gedoelstiasis) in cattle in 1962. This discovery is particularly remarkable when one considers that the research work was conducted in the field and that the larvae of Gedoelstäti hasseleri and G. cristata, that cause the disease and which he observed with the naked eye, are only 0.7–0.9 mm in length. He also elucidated the pathogenesis of the disease and incriminated the blue wildebeest (Connochaetes taurinus), in which the parasite is able to complete its life cycle without doing much damage, as the source of infection for cattle (Basson, 1962).

Bigalke (Figure 20) succeeded in growing Besnoitia besnoiti, the cause of ‘olifantsvelsiekte’, in cell culture in 1962 – the first protozoan parasite to be cultured thus at Onderstepoort – which facilitated the development of a vaccine a few years later (Bigalke, 1962).

Of crucial importance for research at Onderstepoort was the establishment of a Molecular Biology laboratory through the initiative of Verwoerd (Figure 21) in the early 1960s. The scientific achievements emanating from this laboratory (see later) placed the Institute on a par with similar laboratories in much more developed countries than South Africa.

In 1968 Bigalke published his research on the epidemiology of bovine besnoitiosis in which he demonstrated that the disease could be transmitted mechanically by a number of
bloodsucking insects, such as tabanids (*Tabanus* spp.), tsetse flies, stable flies (*Stomoxys calcitrans*) and even mosquitoes (*Culex* spp.), from chronically infected to susceptible cattle. This followed on his discovery, by sub-inoculation of skin suspensions into rabbits and cattle, that chronically infected cattle showing the typical clinical signs of the disease and harbouring millions of minute, cystozoite-filled cysts in the dermis were not dead-end hosts but a potential source of infection. The discovery of a *Besnoitia* spp. in blue wildebeest in the Kruger National Park by McCully et al. in 1966 paved the way to vaccine development. A blue wildebeest strain was isolated in cell culture and surprisingly only caused a mild infection when injected into cattle, which were then cross-protected from the clinical form of the disease in the field. This led to the development of a cell culture vaccine containing live organisms of the blue wildebeest strain by Bigalke et al. in 1974 (Bigalke & Prozesky, 2004).

RESEARCH FROM 1968–1980 WHEN DR K.E. WEISS WAS DIRECTOR OF VETERINARY RESEARCH

Weiss, also a recipient of the Theiler Medal (in 1943), became an excellent virologist who, however, was equally at home in physiology, having obtained his doctorate in that discipline with a highly-rated thesis based on research on the cause of bloat (Weiss, 1953a,b).

Anna Verster (Figure 22) conducted taxonomic and other studies on cestodes: her taxonomic revision of the genus *Echinococcus*, published in 1965, and the genus *Taenia*, published in 1969, as well as the development of a method for using the golden hamster as definitive host for *Taenia solium* and *Taenia saginata*, in the early 1970s, are highly regarded internationally.

One of the first of many fine achievements by the Molecular Biology section was the demonstration by Verwoerd in 1969 that the genomes of orbiviruses such as the BTV and AHSV consist of double-stranded RNA. This was followed by clarification of orbivirus structure and replication and the demonstration of the immunogenicity of a single BTV capsid protein (Figure 23) (Verwoerd, 2000; Verwoerd & Erasmus, 2004; Coetzer & Guthrie, 2004).

The aetiology of ‘jaagsiekte’ (ovine pulmonary adenomatosis, a lung cancer of sheep) was finally elucidated when Verwoerd and his team succeeded in isolating a retrovirus from affected sheep. Control of the disease, however, remains difficult because the absence of a humoral immune response complicates the detection of chronically infected animals for culling purposes and the development of a vaccine. Later it was found that the phenomenon of the absence of an immune response was due the presence of an endogenous form of the virus in the genome of all sheep (Verwoerd et al., 2004).

Naudé (Figure 24) and Potgieter set the tone in 1971 for future basic research (see later) on the chemical structure of the toxins of already known and newly discovered poisonous South African plants when they elucidated the structure of the toxins of tulp (*Homeria pallida* = *H. glauca*). They found that it contains bufadienolides, which are cardio-active glycosides (Kellerman et al., 1988).

Erasmus (Figure 25) revolutionised the production of vaccine against AHS when he started applying the plaque-selection method of selecting suitable virus strains from field isolates in 1974. Large plaques were selected for this purpose. After
meticulous testing of candidate strains for innocuity and immunogenicity, the currently used polyvalent vaccine, which contains the eight most common strains of AHSV, was produced (Coetzer & Guthrie, 2004).

Cameron (Figure 26) first conducted fundamental research on the antigenicity of Corynebacterium spp. in the early 1970s and then went on to develop vaccines against Corynebacterium ovis and Corynebacterium pyogenes that are still in use unchanged today (Cameron et al., 1972).

Good progress, the first of significance since the time of Theiler, was made with local research on redwater (babesiosis) and gallsickness (anaplasmosis) of cattle. Potgieter (Figure 27) and co-workers conducted a series of elegant studies in the 1970s on the life cycle of Babesia bigemina and B. bovis (first diagnosed in South Africa by Neitz in 1941 although probably present much earlier) in the vector ticks and in cattle, which included studies on the fine structure of the parasites. This fundamental research placed the more practical studies that were to follow on a sound scientific footing (see later).

Weiss was made responsible for implementation of the government’s decision to transfer the Onderstepoort Faculty in its entirety to the University of Pretoria – it had been partially independent from the Institute since 1958 – which took place in 1973. The decision that the existing links between the Department of Agriculture and its agricultural faculties – of which the Onderstepoort Faculty was one – should be severed, applied to all the local universities concerned. There was considerable doubt in the minds of many people about the sagacity of such a drastic development. They argued that it would not only cause a duplication of certain disciplines such as toxicology, infectious diseases, parasitology and pathology, which would probably lead to dilution of manpower at the Institute, but that the tremendous advantages of having expert research scientists from the Institute, who were continually dealing with field problems in these disciplines, as teachers would, more importantly, largely be lost. Both fears were realised, but it was only in the 1990s that depletion of the research staff at the Institute became a serious problem.

Solanum kwebense, a small shrub known colloquially as the ‘bitterappel’, was identified in 1976 by Pienaar, Kellerman and co-workers as the cause of a previously unknown neurological disorder (‘maldronksiekte’) characterised by epileptiform seizures and signs of cerebellar dysfunction (Figure 28). The disease has only been recognised in the northern and northwestern Transvaal, now North West and Limpopo provinces, respectively, and is encountered when there is a serious shortage of normal pasture, cattle therefore being forced to feed on the shrub to gain some sustenance (Kellerman et al., 1988).
In the late 1970s, Barrowman conducted a thorough investigation on the pathogenesis of dourine, a venereal disease, after natural infection of horses at the laboratory and artificial intra-spinal infection. He followed the pathogenesis in relation to the distribution of the causative trypanosome (*Trypanosoma equiperdum*) in the body at various stages of the sequence of clinical events that develop after natural infection and found that transmission is more likely to occur when a recently infected stallion or mare is involved as vector. Although parasites are present in the blood, they are rare and centrifugation of blood is necessary to demonstrate them. Parasites are also present in small numbers in the discharges from the genitalia. The onset of the nervous form of the disease coincides with the presence of the parasites in the cerebrospinal fluid in which parasites can sometimes be sufficiently plentiful to be demonstrated microscopically (Luckins et al., 2004).

Mouldy maize residues originating from the production of sorghum beer were identified for the first time in South Africa in 1976 as the cause of high mortality associated with muscle tremors and paralysis in cattle fed on this by-product. Tremorgenic mycotoxins produced by the fungus *Aspergillus clavatus* were incriminated (Kellerman et al., 1988).

**RESEARCH FROM 1980 – 1988 WHEN DR R.D. BIGALKE WAS DIRECTOR OF VETERINARY RESEARCH**

Bigalke, a protozoologist, for the greater part of his research career worked with that great multi-disciplinarian Neitz, whose research perforce became confined to the unicellular animal parasites and tick toxicoses when discipline-based research sections became the structural norm at the Institute. As Director, Bigalke strongly promoted research on resistance of indigenous livestock to infectious diseases and tick infestation i.e., easy care animals (Bigalke, 1976; Bigalke, 1981).

One of the most exciting research highlights in the 1980s was the cultivation of *Ehrlichia ruminantium* (then *Cowdria ruminantium*), the cause of heartwater in domestic ruminants, in cell culture by Bezuidenhout (Figure 29) and co-workers in 1985. It was the first rickettsial organism to be grown *in vitro* in a calf endothelial cell line at Onderstepoort (Figure 30). This paved the way for the molecular biological studies by Allsopp on the major antigenic proteins and their genes of the micro-organism (see below). Bezuidenhout also organised an extremely fruitful international scientific congress on heartwater entitled ‘Heartwater: Past, Present and Future’ which took place in the conference centre at the tourist camp Berg-en-Dal in the Kruger National Park from 8–11 September 1987. The proceedings were published under the names of the various authors as a special issue of the *Onderstepoort Journal of Veterinary Research* (1987), Vol. 54, No. 3, pp. 161–546. Despite the then existing political isolation of South Africa, heartwater researchers from all over the world, including various African countries, France and its Caribbean islands, the USA, the United Kingdom and Germany, attended. The conference not only provided a forum for ample discussion, but the current state of scientific knowledge was catered for by the 59 papers presented. A final contribution on future prospects and goal setting guided the future direction of heartwater research.

Du Plessis (Figure 31) developed an indirect fluorescent antibody test for heartwater in 1981 using the Kümm stock of *E. ruminantium* passaged in mice as antigen, the organisms occurring in peritoneal macrophages. Kümm had isolated this strain in 1971. Further studies by Du Plessis and various co-workers added significantly to our knowledge on the epidemiology and immunology of the disease (Allsopp & Bezuidenhout, 2004).
The early redwater vaccine developed against *B. bigemina* by Theiler in ca. 1912 and that against *B. bovis* by Neitz consisted of defibrinated or citrated blood drawn from donor-carrier cattle.

The vaccine suffered from variable infectivity and poor quality control. This was changed by De Vos (Figure 32) in 1973 who developed a chilled, combined vaccine from acutely infected, spleen-necrotised calves containing a standardised number of *B. bigemina* and *B. bovis* organisms per millilitre using less pathogenic strains. The vaccine was further improved in the 1980s and eventually replaced by De Waal and Combrink in 1998 with standardised, frozen, separate *B. bigemina* and *B. bovis* vaccines, which could be subjected to full quality control procedures prior to use (De Vos et al., 2004).

The Theiler isolate of *Anaplasma centrale* has been used since 1912 as a live vaccine against anaplasmosis. Although generally a mild pathogen, it was shown by Bigalke in 1980 that it can cause severe reactions in adult cattle. For many decades it consisted of blood obtained from recovered carrier cattle, but as in the case of redwater its infectivity was variable and the vaccine therefore unsatisfactory. Since the 1990s the vaccine is issued as a frozen product containing a standardised number of *B. bigemina* and *B. bovis* organisms per millilitre using less pathogenic strains. The vaccine was further improved in the 1980s and eventually replaced by De Waal and Combrink in 1998 with standardised, frozen, separate *B. bigemina* and *B. bovis* vaccines, which could be subjected to full quality control procedures prior to use (De Vos et al., 2004).

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kop’. Exactly why microliths are produced had to await further investigations (see later) (see Kellerman et al., 1988 for a comprehensive review of the above mentioned research).

Further progress was made with molecular biological research on BT. Huismans and Cloete successfully cloned and sequenced genome segments of BTV in 1987 and found that the segments could be used as diagnostic probes to identify BTV directly in blood samples from infected sheep and in cultured cells. Huismans (Figure 37) and co-workers also made progress with the construction of genome libraries in the late 1980s. Good progress has also been made by a team of Onderstepoort and British scientists led by Roy in the construction of recombinant vaccines expressing various BTV proteins using the insect derived baculovirus as vector. For example, the virus-like particles that are formed when insect cells are infected simultaneously with VP2 and VP5 baculovirus recombinants produced high levels of immunity. Unfortunately upgrading the production of these vaccines quantitatively for commercial use has not been achieved yet (Verwoerd & Erasmus, 2004).

The epidemiology of foot-and-mouth disease (FMD) was introduced in the mid 1960s. The availability of a suitable, high containment laboratory at Onderstepoort from 1980 facilitated the development of the necessary technology for typing virus isolates obtained from wild animals. Thomson and his co-workers showed that overt FMD occurred most commonly in the impala (Aepyceros melampus) and that SAT 1, SAT 2 and SAT 3 strains were involved. The question, however, was: how did the impala get infected? The role of African buffaloes, known to be healthy carriers of the virus and long thought to be the most important source of infection for other animals and thus the source of new outbreaks, in the epidemiology of the disease was thoroughly investigated. This was possible because the technology to distinguish between intra-typic variants of SAT viruses by gene sequencing was established by Thomson (Figure 38). Genome sequencing studies showed that buffaloes are the usual source of infection of impala, which are not persistently infected. Young buffaloes get infected from carrier animals, such as their dams, when colostral immunity starts to wane at 2–4 months of age with the result that minor epidemics of subclinical infection occur in breeding herds. It is at this time that such herds are probably a source of infection for other susceptible species such as impala or even cattle. Using genome sequencing, Vosloo and her team have recently been able to trace the source of outbreaks in cattle to their origin in specific buffalo populations (Thomson & Bastos, 2004).

Equine influenza was unknown in South Africa until 1986 when it was introduced from overseas, seriously affecting the racing industry. The technology used to produce an inactivated vaccine against the disease was available due to the foresight of Erasmus who had previously imported the relevant strains, enabling him to produce a vaccine in sufficient quantities to control the disease within weeks of its first diagnosis (Verwoerd, 2000).

The aetiology and epidemiology of the occurrence of epididymitis in virgin young rams maintained intensively on a high plane of nutrition has created considerable confusion and even controversy. In his studies on the aetiology and epidemiology of ram epididymitis, Jansen came to the conclusion that the disease was caused by a hormonally influenced, ascending infection of bacteria such as Actinobacillus seminis and Histophilus ovis, which he regarded as normal flora of the intestinal tract (Jansen, 1980; 1983). It is thought by some

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Figure 36. Microliths blocking the bile ducts in a sheep with geeldikkop. Photograph reprinted from Plant Poisonings and Mycotoxicoses of Livestock in Southern Africa with permission by Oxford University Press Southern Africa, Cape Town.

Figure 37. H. (Henk) Huismans not only cloned and sequenced genome segments of the bluetongue virus, but also developed diagnostic probes for the disease. Courtesy of the University of Pretoria.

Figure 38. G.R. Thomson was the eleventh Director of Onderstepoort. He had previously managed its Foot-and-Mouth Disease Laboratory and unravelled the epidemiology of the disease in the Kruger National Park by using elegant gene sequencing techniques.
Genetically determined resistance of livestock and wild animals to infectious diseases has received considerable research attention in countries like South Africa, other African countries and Australia since the 1940s. One of the best-known examples is the trypano-tolerance shown by certain breeds of cattle, such as the N’Dama in West Africa, to trypanosomosis. Bonsma was one of the first South African scientists to observe the superior resistance of indigenous breeds of South African cattle, like the Afrikander – a Sanga-type of Bos taurus – to tick-borne diseases like heartwater and tick-infestation in the field in 1944. Bonsma not only propagated the use of Sanga breeds of cattle by South African beef farmers but also developed an artificial breed from the Afrikander that was later called the Bonsmara. Spickett was first to compare the resistance of Nguni (an indigenous Sanga breed), Bonsmara and Hereford cattle to infestation with Boophilus microplus ticks experimentally at Onderstepoort. The Nguni proved to be highly resistant, the Bonsmara intermediate and the Hereford highly susceptible. Useful criteria for further improvement of genetic tick resistance in the Nguni and Bonsmara breeds were identified (Spickett, 1994).

Van Wyk’s (Figure 39) studies on the cryopreservation in liquid nitrogen of roundworm larvae facilitated his research conducted over several years on various aspects of verminosis. His investigations on the infectivity and development of L3 larvae of Haemonchus contortus (wireworm), Trichostrongylus colubriformis and T. axei, which were stored in the frozen state for many years – some for more than 15 years – showed that freezing was a very satisfactory method to maintain nematode larvae. It was far superior to the laborious and expensive method of cycling worm strains through their final hosts (Van Wyk & Gerber, 1980; Van Wyk et al., 2000).

D.G. Steyn’s textbook entitled The Toxicology of Plants in South Africa, which appeared in 1934, was very useful and served its purpose for many years. However, it was totally eclipsed in quality by the magnificent work produced by Kellerman, Coetzer and Naudé entitled Plant Poisonings and Mycotoxicoses of Livestock in southern Africa, which was published in 1988. This highly informative and comprehensive standard work of reference was recently updated, and the 2nd edition published in 2005.

RESEARCH FROM 1988–1998 WHEN DR D.W. VERWOERD WAS DIRECTOR OF VETERINARY RESEARCH

Verwoerd made molecular biology his field of study with great determination from the very outset of his career. He managed to secure several prestigious fellowships that enabled him to further his studies at leading overseas research institutions such as the Max Planck Institutes for Virology and Biochemistry in Germany and the National Cancer Institute in Bethesda, USA. He founded the first Molecular Biology research group in South Africa in 1964, which has since developed into one of the leading molecular virology laboratories, anticipating the tremendous influence that the newly developed molecular techniques would have on all biological research. By 1989 the impact of the new gene technology could be seen in many diverse fields. Genome libraries have been constructed for a number of viruses and haemoparasites and genes identified which can be used for the diagnosis of diseases such as BT, AHS, equine encephalosis, babesiosis, anaplasmosis, theileriosis and heartwater, either as molecular probes or in PCR tests.

Genes for bacterial toxins have been cloned and expressed, assisting in the production and evaluation of vaccines. Subtyping of FMD viruses by RNA sequencing have been described above and a similar approach identified many subtypes of E. ruminantium. Immunogenic proteins have been identified in various organisms and putative recombinant vaccines constructed. The possibilities seemed endless.

Major restructuring, which had a dramatic influence on the staff component of the Institute, occurred in 1992. It was separated from the vaccine factory (named Onderstepoort Biological Products) and the FMD laboratory and transferred from the Department of Agriculture to the newly created Agricultural Research Council (ARC) together with the 12 sister research institutes involved in agricultural research. Owing to a drastic decrease in government funding over the following 10 years it was necessary to reduce the staff component, cut back on research expenditure and seek external funding. A drastic change in corporate culture, from science-driven to client-driven research became necessary. It was partly achieved by restructuring the research effort into 18 programmes, each driven by a programme leader, and interdisciplinary in nature.
Unavoidably the emphasis in these programmes shifted from long-term basic to short-term applied research and services such as diagnostics, as required by its clients. Nonetheless, OVI (Onderstepoort Veterinary Institute) managed to continue making major scientific advances. York and his team elucidated the complete genomic nucleotide sequence of the exogenous ‘jaagsiekte’ virus, which is transmitted horizontally, in 1992. It constituted the first complete sequencing of a genome by a South African scientist, facilitating further research on its oncogenicity, and possibly improved control measures. An endogenous form of ‘jaagsiekte’ virus, which is transmitted vertically, was also demonstrated and a molecular probe developed to distinguish it from the exogenous virus.

Further progress was made in clarifying the aetiology of ‘geeldikkop’. It was established in 1991 by Kellerman and co-workers that geeldikkop could be induced by dosing crude steroidal saponins from T. terrestris to sheep in the absence of sporidesmin, the latter having previously been shown to be a predisposing factor (see earlier). It is currently believed that not all saponins are lithogenic, i.e., produce crystals in the bile ducts. There now seems to be consensus that ‘geeldikkop’ is not a mycotoxicosis. However, the sporadic toxicity of T. terrestris remains unexplained (Kellerman et al., 2005).

A frustrating problem in the diagnosis, epidemiology and control of malignant catarrhal fever in cattle has been the fact that it was impossible to determine with any certainty whether the source of infection of such animals was wildebeest [blue and black wildebeest (Connochaetes gnou)] or sheep. This was one of the arguments used by game farmers and other pressure groups in South Africa that led to the abolition of government control over the movement of wildebeest in 1993. The result has been an alarming increase in the incidence of the disease resulting from the unrestricted movement of large numbers of wildebeest in particularly the Limpopo, North West and Free State provinces. Michel developed a diagnostic probe in 1993 that can distinguish between wildebeest- and sheep-associated forms of the disease (Reid & Van Vuuren, 2004). As was expected, application of this test to field cases has shown that wildebeest are a much more common source of infection for cattle than sheep. If the small number of wildebeest in South Africa is compared to the millions of sheep it is clear that the risk of infection of cattle by sheep is virtually negligible. Several cattle farmers have now been enabled by the new diagnostic capability to obtain court rulings against neighbouring game farmers granting them compensation for the cattle losses sustained (Wessels, 2007).

In South Africa, endemic rabies is associated with the distribution of the yellow mongoose, a well-documented maintenance host for rabies virus. However, antigenic and nucleotide sequence analyses by Nel et al., (1998) have shown that two different biotypes of rabies virus exist in South Africa. One is transmitted by dogs and other Canidae (dog rabies); the other, apparently indigenous, group of heterogenous viruses are transmitted by Viverridae (viverrid rabies) (Swanepoel, 2004).

The newly developed molecular techniques allowed a detailed epidemiological study of the two viruses and also led to the development of an oral bait vaccine for feral dogs in collaboration with field workers.

Maedi-visna was first described in South Africa in 1915 by Mitchell and named Graaff-Reinet disease. It was initially regarded as an aberrant form of ‘jaagsiekte’ but De Kock (1929) realised that they were two distinct diseases. The name maedi-visna – derived from the two most common forms of the disease – was coined in Iceland where most of the research on the disease has been done. It was rediscovered in South Africa in 1986 by isolation of the virus from a sheep suffering from ‘jaagsiekte’ and a recombinant ELISA test, which was commercialised, was developed for its diagnosis (Verwoerd & Tustin, 2004).

Van Dijk (Figure 40) and her team made progress with the development of subunit vaccines against AHS using recombinant DNA technology. A baculovirus was used to express serotype 5 VP2 (viral protein) of AHHSV. A subunit vaccine produced thus proved to be immunogenic and protected horses against a challenge infection. The immunity was, however, strain specific and, apart from some technical difficulties that still have to be solved, it will clearly be necessary to include multiple viral proteins in such a vaccine to provide adequate protection in the field (Coetzer & Guthrie, 2004). The demonstration by Barnard that zebras (Equus burchelli) in the Kruger National Park can act as passive carriers of the virus provided a solution for the old problem of how the virus overwinters (Barnard, 1993).

Severe infection of maize with the fungus Diplodia maydis, a common but usually a hardly noticeable pathogen, sometimes occurs under favourable climatic and managerial conditions. The fungus has been shown to produce a neurotoxin. If cattle and, to a lesser extent, sheep ingest infected material on harvested maize lands they may develop a disease which has been named diplodioidosis and is characterised by ataxia, paresis and paralysis. Hitherto it has been necessary to feed naturally infected maize to experimental cattle or sheep in order to conduct research on this neuromycotoxicosis. However, Snyman recently (2003) succeeded in developing a guinea pig bioassay system which he used to identify the neurotoxic principle(s) in a culture purified by column chromatography (Kellerman et al., 2005).

The disease called ‘gousiekte’, which is caused by certain plants of the family Rubiaceae, has been known for many...
Jane Walker (Figure 41) followed in the footsteps of Getrud Theiler when she joined the Institute in 1966 to become one of the most authoritative tick taxonomists. With Keirans and Horak, she authored the definitive taxonomic work on the brown ticks or *Rhipicephalus* species of the world in the late 1990s (Walker et al., 2000).

Following an unprecedented outbreak of BT in southern Europe, a collaborative five-nations programme, funded by the EU, was launched to study the biosystematics, seasonality, distribution and vector competence of *Culicoides* midges. An additional vector of this disease was discovered. Whereas 22 *Culicoides* spp. were known in 1951, no fewer than 120 are recognised today (R. Meiswinkel, pers. comm., 2006).

Van Wyk blew the whistle on the over-exploitation of anthelmintics in the sheep-farming areas of South Africa, resulting in widespread development of resistance of certain nematodes to many of these drugs, thereby constituting a major problem for successful control of intestinal parasites in this country (Van Wyk et al., 1997). He followed this up with research, confirmed under farming conditions, in which sheep are cleared of infection with resistant helminths and then artificially infected with susceptible ones for seeding of the pastures concerned with their eggs (Van Wyk & Van Schalkwyk, 1990). Following this up with management systems based on pasture rotation and alternative grazing of the pastures by sheep and cattle, further reduced the need for dosing with anthelmintics.

Major advances have been made by Malan, Van Wyk (formerly of the Institute) and other co-workers with research on the integrated control of internal parasites, *inter alia* by the application of the FAMACHA technique, which is a practical method for farmers to identify sheep with anaemia caused by severe wireworm infestations, thus limiting the use of anthelmintics. This technique is also used for the identification of highly susceptible sheep for culling purposes in order to establish genetically resistant (easy care) strains of the animals (Malan & Van Wyk, 1992; Malan et al., 2001).

To meet the requirements of clients for improved diagnostics a PCR laboratory was set up in 1994 to develop and apply PCR and ELISA tests. A large number of these tests for a variety of pathogenic organisms, including viruses, bacteria and bacterial toxins as well as haemoparasites were developed for use by the Institute and in a few cases were also commercialised. The laboratory formed part of a new Division for Applied Biotechnology, which also became involved in the development of recombinant vaccines.

A serious event was the discovery of bovine tuberculosis in buffalo in the KNP (reported in 1991 by Bengis et al.) and its spread to other wildlife at a later stage. The classic skin test for TB in live domestic animals could not be applied to wildlife, years. Walker in 1908 to 1909 described the typical clinical sign of animals – in his case, sheep – either dropping dead in their tracks or being found dead, hence the Afrikaans name meaning ‘quick disease’. The cause of death is acute heart failure caused by a chronic heart lesion, i.e., endocardial fibrosis. The toxin responsible for ‘gousiekte’, pavetamine, was isolated by Fourie in 1994 and its chemical structure determined by Vleggaar of the University of Pretoria in 1997. Moreover, in 2001 Schultz and co-workers found that mice are susceptible to pavetamine and that it inhibits protein synthesis in the heart. This results in depletion of myosin and could explain the occurrence of heart failure (Kellerman et al., 2005).

An extensive study of factors affecting udder health in the South African dairy cow by Giesecke and co-workers culminated in a series of 36 publications. The discovery that heat stress was a predisposing factor to mastitis had an important impact on the dairy industry (Du Preez et al., 1990).

Biting of sheep by blackflies (*Simulium* spp.) caused considerable economic losses to farmers along the banks of some of our rivers, especially the Gariep River with its many dams. Initial attempts instituted by C.J. Howell to control these river-breeding insects by manipulating the water level failed because of irrigation requirements. Entomologists from Onderstepoort then developed a successful procedure in which two larvicides were applied to the river at specific intervals. The Institute implemented this successful control programme under contract for the Department of Agriculture for a number of years (Verwoerd, 2000).
necessitating research on alternative diagnostic methods. In collaboration with researchers in the KNP and the University of Pretoria’s Faculty of Veterinary Science, a PCR, an ELISA and eventually also a gamma-interferon test were developed for this purpose providing a boost to the various research projects on TB in wildlife.

A milestone in the history of Onderstepoort was its appointment in 1993 as the OIE (International Office for Epizootic Diseases) Regional Collaborating Centre for Africa. Its expertise had also been recognised previously by the selection of six of its units as International Reference Laboratories for important animal diseases.

A number of new vaccines were developed during this period. A safe, effective, attenuated (live) vaccine for calf paratyphoid caused by *Salmonella typhimurium* constituted the first vaccine against this organism produced by curing it of its virulence plasmid. Odendaal and his group (1993) also developed a leukotoxin vaccine against pasteurellosis, which is produced by Onderstepoort Biological Products in a monovalent Leukopast I and a trivalent Leukopast III form, the latter specifically for the feedlot industry. Several recombinant viral vaccines were developed, inter alia a fowl pox/Newcastle disease recombinant, which is in the process of evaluation as a vaccine against the latter disease, and lumpy skin disease virus (LSDV) recombinants with AHSV, bovine ephemeral fever virus and Rift Valley fever virus. The latter recombinant has been shown to be as effective, if not more so, than the existing Smithburne, live, attenuated vaccine. For various reasons, including cost, none of these have reached the production stage yet.

A world first was the isolation of equine arteritis virus from donkeys (*Equus asinus*) by Paweska et al. (1995). The disease was known to be limited to a small, isolated group of horses in South Africa but the widespread occurrence of a subclinical infection in donkeys was unexpected and caused quite a stir amongst horse breeders. Fortunately it does not spread from donkeys to horses.

M.W. Henning’s internationally acclaimed textbook *Animal Diseases in South Africa*, of which editions appeared in 1932, 1949 and 1956, was in dire need of being updated. Henning’s illness and death in 1962, when he had already started with this arduous task, regrettably made this ideal unrealisable.

Moreover, the field had expanded beyond the scope of a single author. J.A.W. Coetzer (Figure 42) and his co-editors consisting of G.R. Thomson, R.C. Tustin and N.P.J. Kriek, plus a formidable team of authors, took up the challenge. A two-volume book entitled *Infectious Diseases of Livestock with Special Reference to southern Africa* appeared in 1994. In the mean time the first edition was exhausted and a second one, this time edited by Coetzer and Tustin of the Onderstepoort Faculty, but assisted by amuch larger team consisting of 197 specialist authors, was published in 2004. The new edition, consisting of three volumes and entitled *Infectious Diseases of Livestock*, no longer limits itself to southern Africa but covers most infectious diseases of livestock. It is the most comprehensive book on infectious diseases of livestock currently available.


Since 1998 the OVI has gone through uncertain times. This has been accompanied by a quick succession of directors and lately also in a change of the title of the head of the Institute. The research highlights pertaining to this period will therefore be dealt with collectively. At the end of 1998 the ARC-OVI and the ARC-Institute for Exotic Diseases were amalgamated under the leadership of G.R. Thomson. In his words (Biennial Report of the ARC-OVI for 1998–2000) molecular approaches to vaccine development and epidemiology continued as the main focus of research at the combined institute. Laboratory diagnostics remained a mainstay of its activities, however, and two new laboratories were established to meet the needs of the government. The first is responsible for the routine screening of specimens for bovine spongiform encephalitis (‘mad cow disease’), in order to maintain the country’s certification of freedom from the disease. The second is accredited for the sophisticated tests for drug and other
residues in animal products required by the EU and other countries for import purposes.

Considerable progress has been made in recent years with studies on the cultivation of *Ehrlichia ruminantium* (previously called *Cowdria ruminantium*) in cell culture. It has been shown that endothelial cells from a wide variety of sites and several naturally susceptible hosts can be used for this purpose and Zweygarth and Josemans have succeeded in propagating the organism continuously in a canine macrophage-monocyte cell line. Zweygarth and co-workers have also developed a chemically defined culture medium for growing the organism in cell culture. During the course of these studies they moreover discovered an attenuated strain of the organism that has considerable potential as a possible vaccine. Allsopp and co-workers have been closely involved in unravelling the unexpected genetic variability of *E. ruminantium*. It has been shown that at least eight different 16S ribosomal genotypes exist. However, it has not been possible to grow all eight genotypes in culture and some of them may not represent classic *E. ruminantium* (Allsopp et al., 2004).

A major breakthrough in international terms was the completion of the sequencing and annotation of the full genome of *E. ruminantium*. This was an ambitious project, being the largest genome submitted to sequencing in Africa to date, and could only be completed in collaboration with a large international group of scientists. It will allow the identification of specific genes suitable for the eventual development of a stable, safe and effective vaccine for this important disease (Collins et al., 2005).

In the programme for new viral vaccines and diagnostics a technique was perfected for the routine cloning of full-length double-stranded RNA genomes that has been adopted worldwide. Using this technique the first complete set of VP2 genes of all nine AHSV serotypes was obtained which led to a set of molecular probes by means of which a new virus isolate could be fully serotyped in four days compared to several weeks using traditional methods. In a further development a RT-PCR/reverse line blot technique was developed which further reduced the time needed for serotyping orbiviruses to one day.

The applied biotechnology programme received ISO accreditation for its Newcastle disease virus (NDV) diagnostic PCR test and was also appointed as the official laboratory for all avian influenza testing during an outbreak of this disease among ostriches. It also completed the sequencing of the lumpy skin disease virus genome and identified specific genes important for the construction of recombinant vaccines.

Another first for South Africa was the use of a cloned fusion protein gene of NDV as a DNA vaccine, obtaining significant protection. A pox-vectored rabies vaccine was developed which has been accepted for evaluation in the US (Viljoen, 2000).

Bastos (1998) had shown that gene sequencing of SAT-types of FMD viruses (also see earlier) could be used to determine the origin and trace the course of epidemics in various wild and domestic cloven-hoofed animals. Phylogenetic analysis revealed that multiple topotypes of all six FMD serotypes occur in Africa and are geographically linked. This result is relevant to the selection of vaccine strains for specific regions (Thomson & Bastos, 2004).

The recent progress with research on the pathogenesis of 'gousiekte' by Schultz and co-workers was mentioned (see earlier). A new approach to combat the poisoning of livestock was also explored. It has been observed many years ago that animals born and bred in a specific area rarely eat the toxic plants indigenous to that area whereas recently introduced animals are highly susceptible to poisoning. This led to the concept of 'conditional feed aversion' and experiments confirmed that animals can be 'taught' not to eat poisonous plants by adding small amounts of the toxin to their feed. Success was obtained with *Senecio* species but not with other toxic plants, (Kellerman et al., 2005). Another success story in feed related poisoning was the discovery that manganese poisoning, caused by geophagia in calves and lambs in the North West Province, can be treated effectively with iron dextran and vitamin B12 at birth and at 14 days of age.

In a programme called ‘Immunological Approaches to Disease Control’ Du Plessis and co-workers (2004) established a new technique for the production of specific antibodies for the first time in South Africa, thereby replacing the older hybridoma method. It consists of phage-displayed antibody libraries derived from chicken immunoglobulin genes as a source of highly specific diagnostic antibodies. Combined with techniques for the 'engineering' of antibodies to improve their performance, it is an ideal system for the development of improved serological tests and test kits. Commercial companies have supported some of these developments.

Considerable progress has also been made in research aimed at controlling nagana in KwaZulu-Natal. While the targets that were developed for survey purposes were effective
for *Glossina austeni*, they were not for *G. brevipalpis*. In a new approach the possible use of the sterile insect technique (SIT) for eradicating these tsetse flies was investigated with the support of the International Atomic Energy Agency. It is essential to breed the flies in captivity for the production of sterile males by irradiation. Colonies of the East African strains have been established successfully at Onderstepoort but so far local strains have resisted colonisation (Kappmeier-Green, 2004).

African swine fever is a disease with a limited distribution and economic importance in South Africa. In the rest of Africa it is of great economic importance and therefore receives some attention. A PCR test was developed by means of which a diagnosis can be confirmed within four hours and the OVI is also the only laboratory in Africa at present able to cultivate the virus in macrophages. A phylogenetic study revealed seven genotypes in southern Africa and at least 13 genotypes in East Africa (Vosloo, 2004).

The epidemiology of Corridor disease (theileriosis) has recently received attention again following the disturbing detection of cases from various parts of the country. In close collaboration with the Faculty of Veterinary Science, a real-time PCR diagnostic test has been developed which is more sensitive and faster than previous tests. An interesting result obtained so far is that isolates of *Theileria parva* from cattle are genetically homogeneous whereas isolates from buffalo show considerable genetic variation (A.A. Latif, pers. comm., 2005).

**EPILOGUE**

The research priorities of institutions such as the OVI, which derive a considerable proportion of their funds from the government, have been under pressure for several years. The research policy of the ARC, of which the OVI has been a part since 1992, is clearly directed at providing new technology to previously disadvantaged farmers. When it comes to livestock, however, the question can legitimately be asked whether the diseases that burden the beasts of the latter class of farmer are very different from those that affect commercial farmers.

Diseases and management tend to go hand in hand. The overcrowding, overnight kraaling and inadequate nutrition commonly encountered under conditions of communal farming certainly predispose to the occurrence of infectious and parasitic diseases. Use of communal males also creates ideal conditions for the spread of venereal diseases. However, communal farming has been in existence in Africa for many thousands of years, probably as long as livestock have been domesticated. Moreover, these animals have survived, even flourished, despite the complete absence of specific remedies and pesticides to protect them from the ravages of the many internal and external pathogens of Africa to which they have been exposed. The resistance of indigenous breeds of cattle, goats (*Capra hircus*) and sheep has been well researched and documented. Some of it is referred to above. Natural selection has provided Africa with some very valuable genetic material, of which the Nguni breed of cattle is a prime example. Such genes should be nurtured by specific further selection rather than molly-coddled by the application of modern remedies.

What is indeed necessary is research, development and extension on the management practices applied in the communal farming situation and on small farms, the latter now even found close to many cities such as Cape Town, Johannesburg, Vereeniging, Sasolburg and Pretoria. Whether such activities are the responsibility of the OVI is, however, doubtful. Good management will produce healthy livestock, and with easy care animals such as the Nguni, excellent economic results can be obtained with minimal veterinary input costs.

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**REFERENCES**


