Pathology of Hansen's disease. Analysis of 808 autopsy cases (1940-1998) in the National Sanatorium Oku Komyoen, Okayama, Japan

A total of 808 cases of Hansen's disease in the National Sanatorium Oku Komyoen, Okayama, Japan, autopsied in the period of 1940-1998 were pathologically analyzed. The distribution of *Mycobacterium leprae* infection, its complications and cause of death are described.

The content was presented at the 103rd Annual Meeting of the Japanese Society of Pathology in Hiroshima, 2014 (1-D-11).

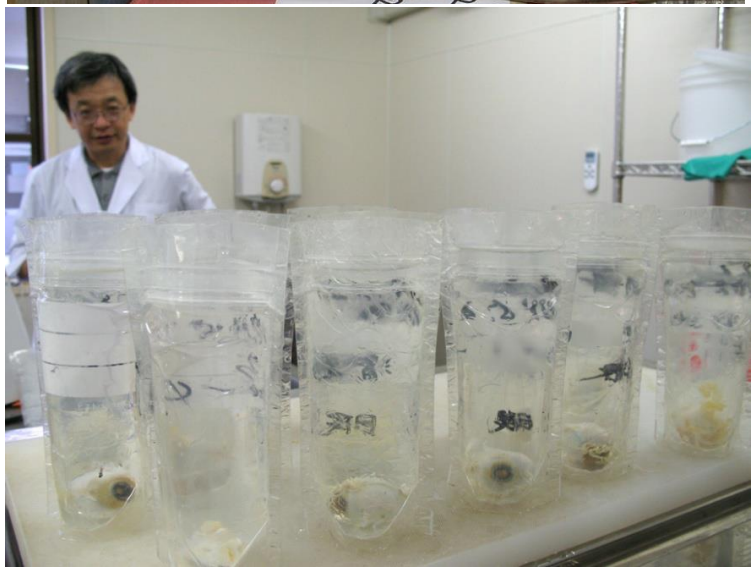
Histological and immunohistochemical analysis of Hansen's disease

More than 800 autopsy cases of formalin-fixed specimens (autopsied in 1940-1998 in Oku-Komyoen, Okayama) were re-sampled in 2006-2008 after long fixation periods up to 67 years.

Immunostaining for the autopsy Hansen's disease

1) Targets: formalin-fixed, paraffin-embedded specimens (fixation periods: 10-67 years)
2) Antigens: BCG (immunostained for all the specimens), HBs antigen, HCV antigen (NS3-NS4, Signet), amyloid A, C3c/IgG/IgA (for nephritis cases), blood group antigens (A, B and H), and bacterial antigens (Staphylococcus, Streptococcus and Pneumococcus)
3) Methods: Amino acid polymer method (pretreatment: heating or proteinase K)

The specimen-keeping room in Oku-Komyoen



Autopsy cases in Oku-Komyoen

Period	number	male	female		M/F	age	median
1940-1945	299	235	64		3.7	43.0 (15～81)	42
1946-1955	143	109	34		3.2	40.5 (13～75)	38
1956-1965	109	74	27	(8)*	2.7	60.2 (26～85)	63
1966-1975	56	43	13		3.3	64.6 (34～86)	64
1976-1985	92	61	31		2.0	68.5 (46～94)	68.5
1986-1998	109	78	31		2.5	76.3 (54～96)	77
Total	**808**	600	200	(8)*	**3.0**	54.4 (13～96)	56

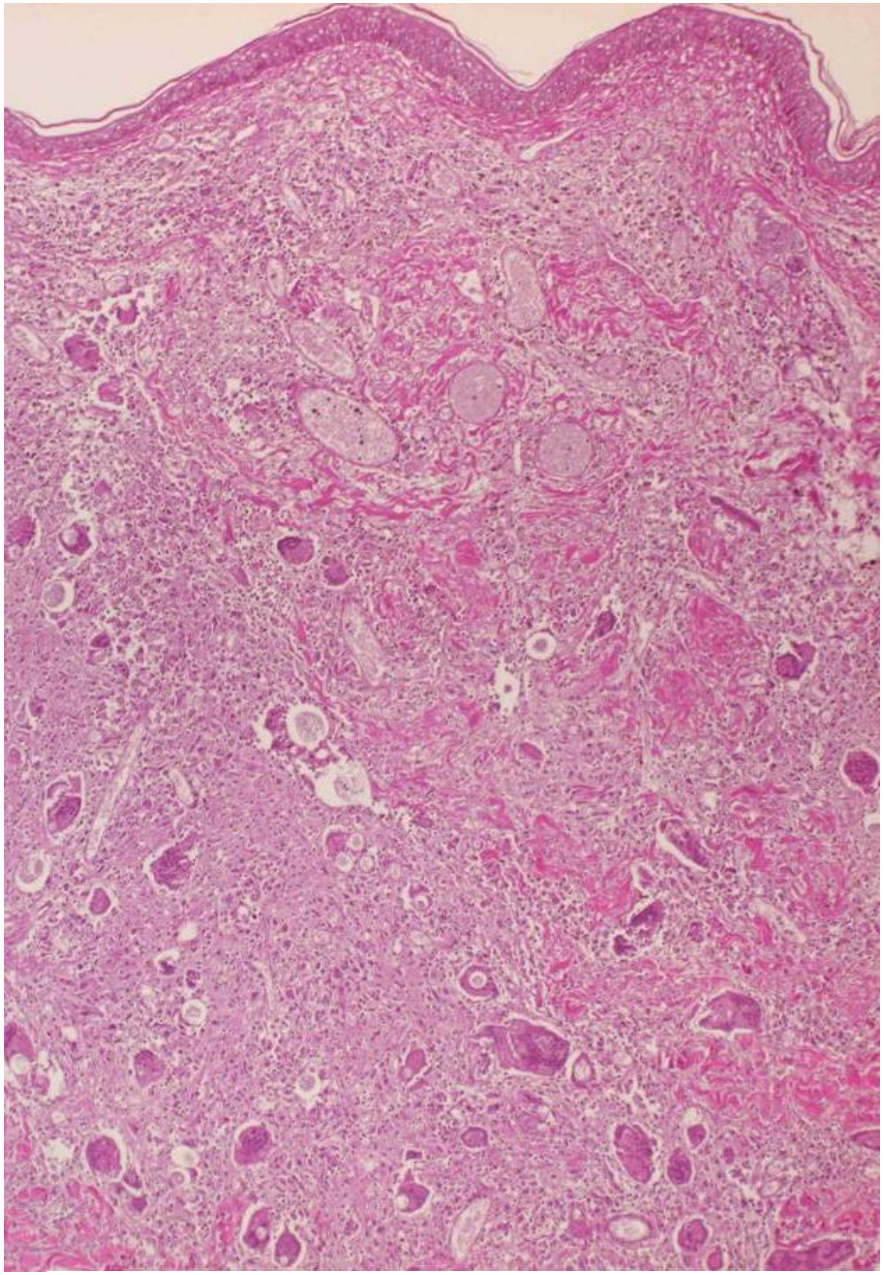
*The sex of 8 cases in 1956-1965 is unknown.
The period of a total of 31 cases are unknown (not included here).
A total of 200 cases up to 1941 are missing.
A total of 84 cases in 1945-1946 are missing because of the endemic of bacillary dysentery (2 cases of bacillary dysentery seen in 1947).
20 cases are missing in 1952-1954.
Cases in 1971-1976 are mostly missing.
Promin injection started to treat Hansen's disease since 1949 in Japan.

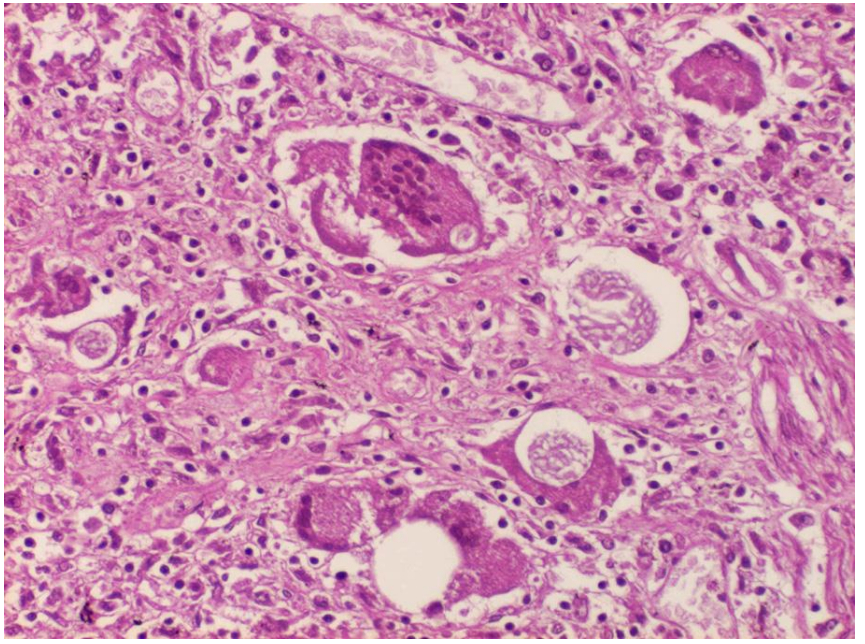
Lesion distribution of Hansen's disease

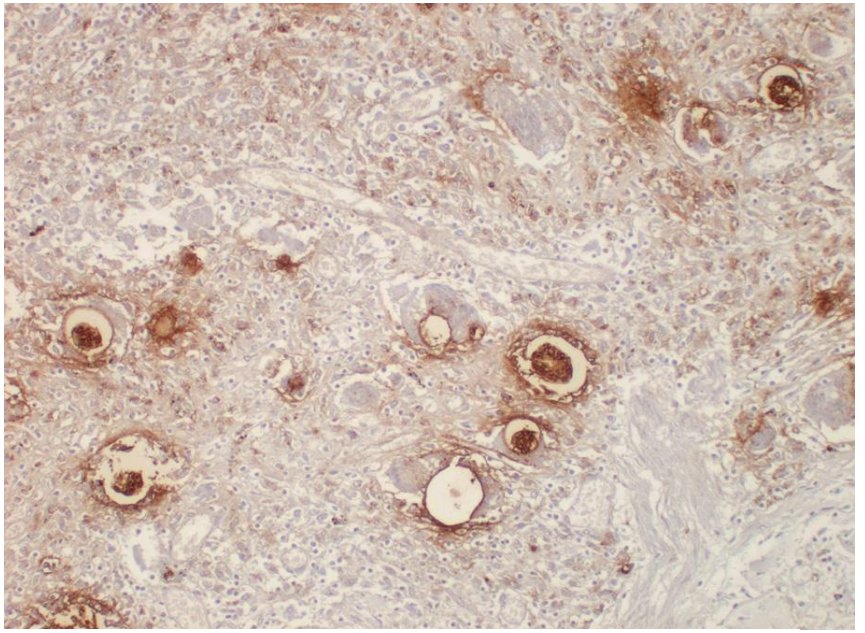
(BCG immunostaining is quite effective)

- **Skin**, especially the distal part of the extremities and face
- **Peripheral nerves** (infrequent involvement of vagal and splanchnic nerves)
- **Central nervous system** (dorsal root ganglion, anterior horn neurons of the spinal cord, hypoglossal nucleus/nucleus ambiguus of the medulla oblongata), infrequently with anterior poliomyelitis and ambiguitis
- **Testis and epididymis** with testicular atrophy and aspermatogenesis
- Eye (anterior eye segments: iris and cornea), occasionally with phthisis bulbi
- **Nasal cavity, pharynx and larynx** (especially the epiglottis), occasionally with laryngeal stenosis
- **Liver, spleen, lymph nodes and adrenals** (leproma formation)
- BCG immunostaining showing **minor lesions** in the kidney, lung, pancreas, heart and salivary glands.
- Little involvements in the thyroid, pituitary, ovary, digestive tracts and placenta.

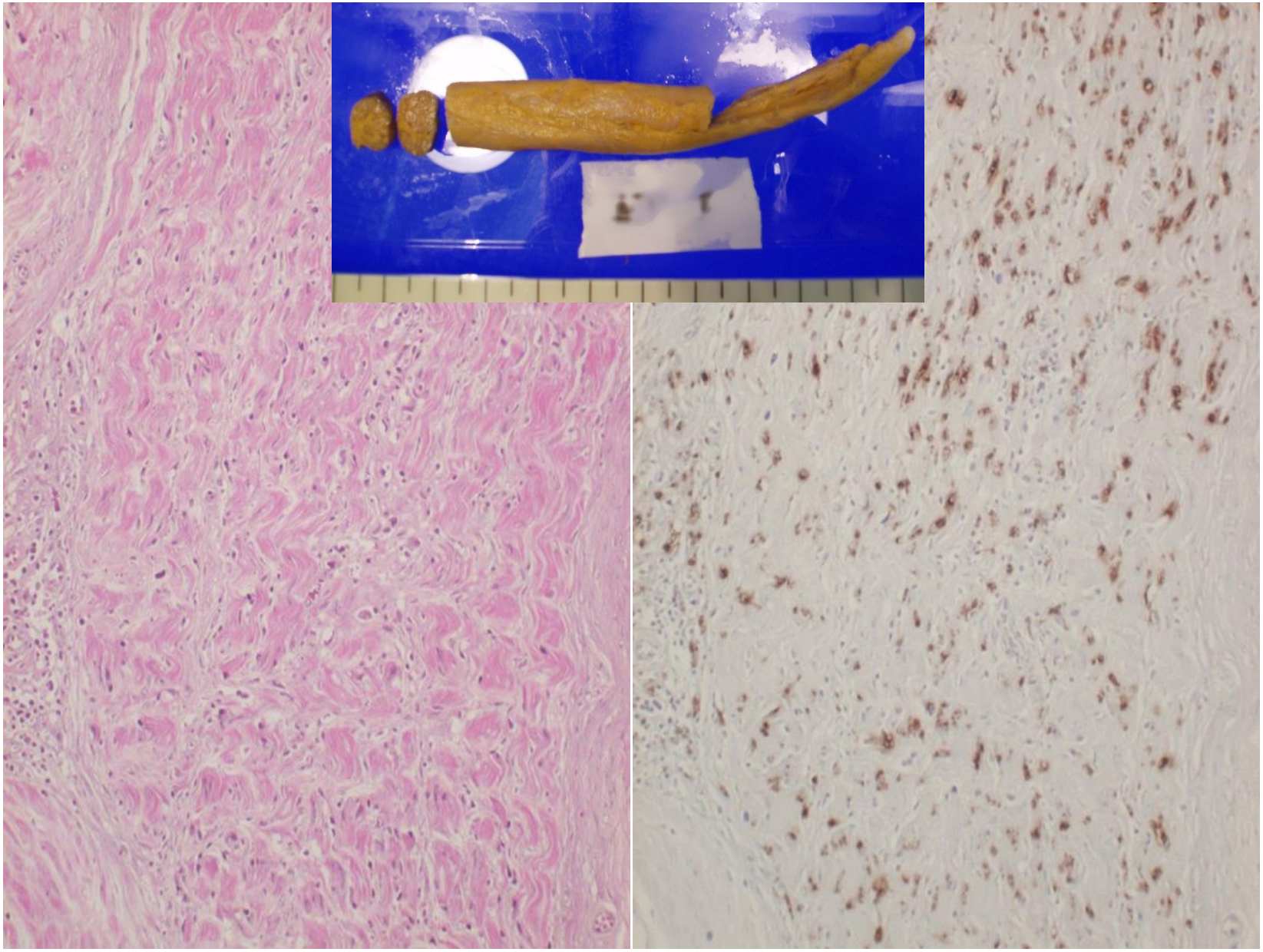
(The distribution of the lesions represents the feature of Mycobacterium leprae, which *is an intracellular pathogen growing in a relatively low temperature.*



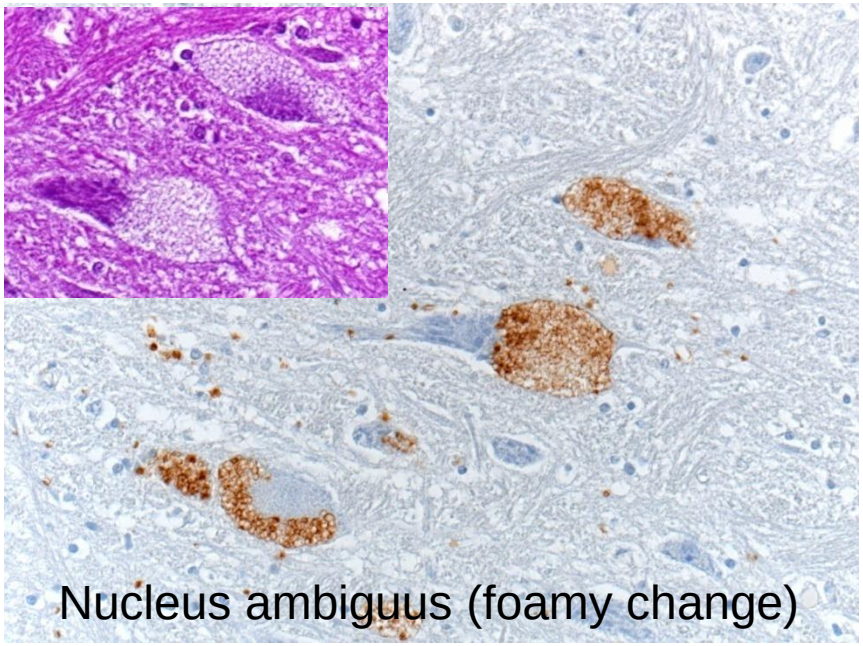


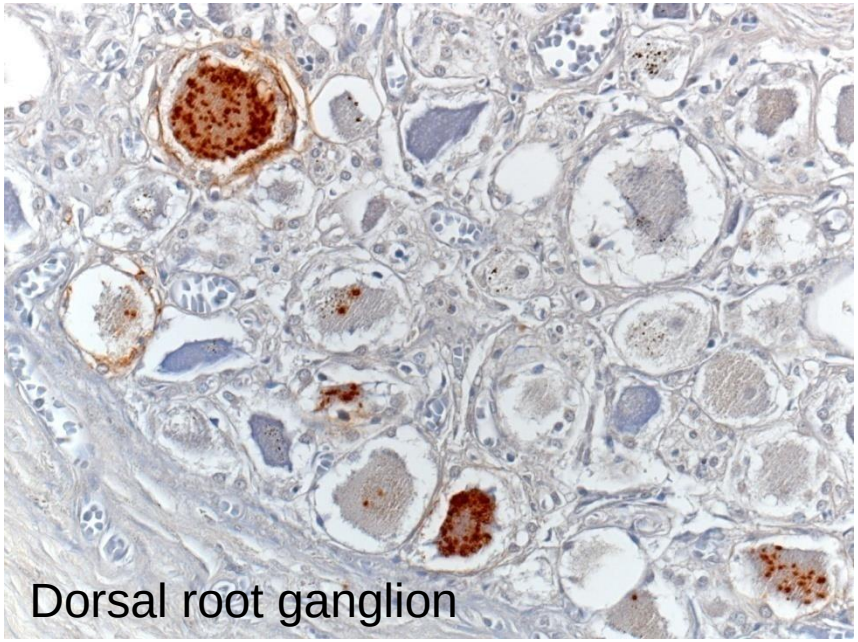


Skin lesions of lepromatous leprosy. In the globi, the mycobacteria are clustered (H&E, right bottom: BCG immunostaining)

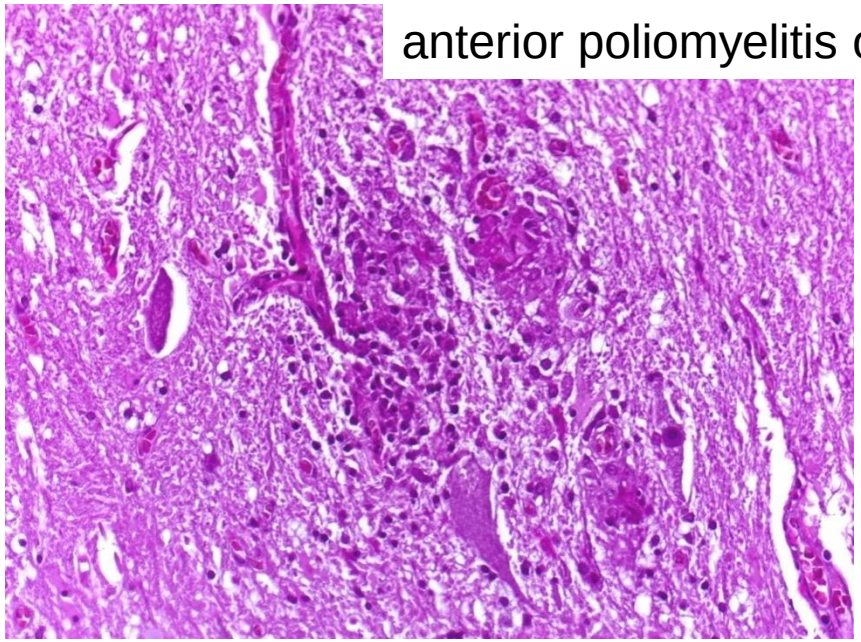


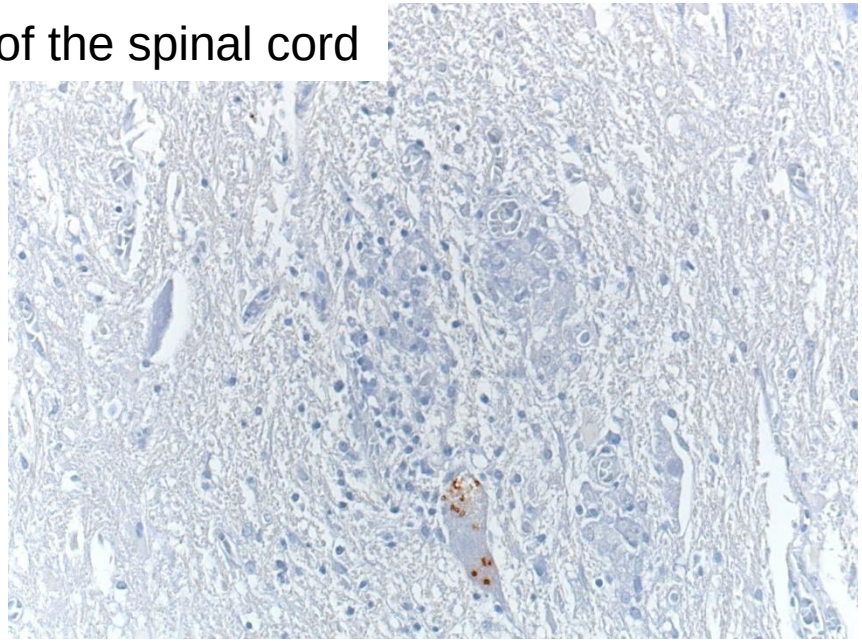
Lepromatous neuritis (upper panel: gross appearance, left: H&E, right: BCG immunostaining) The specimen was fixed in formalin for 40 years.



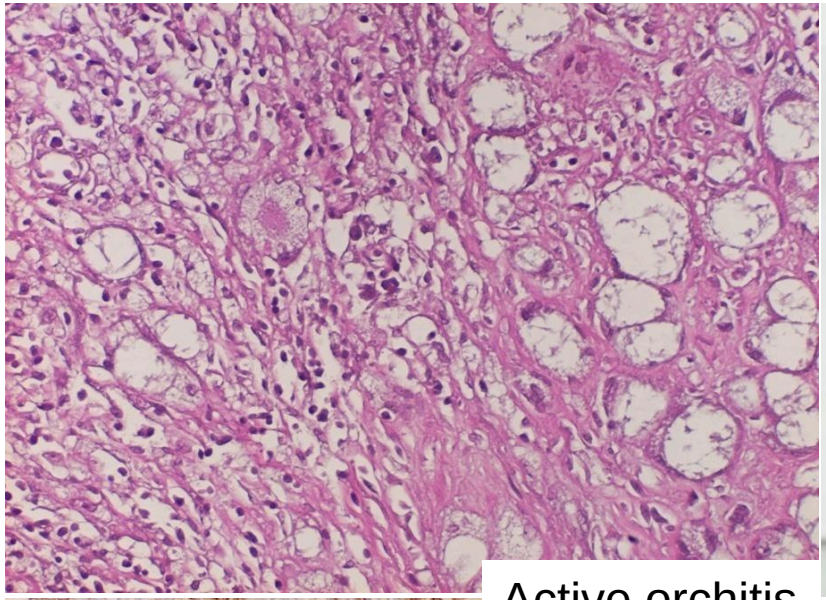


anterior poliomyelitis of the spinal cord

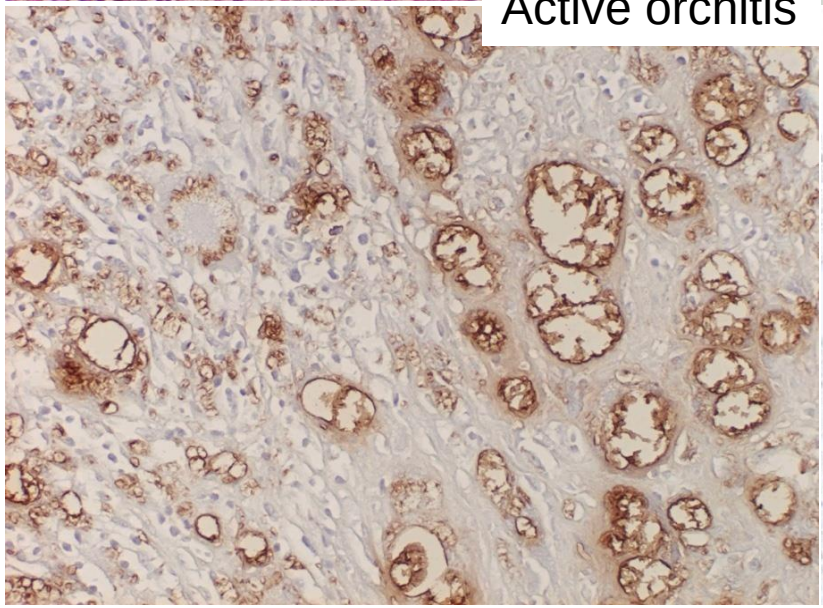


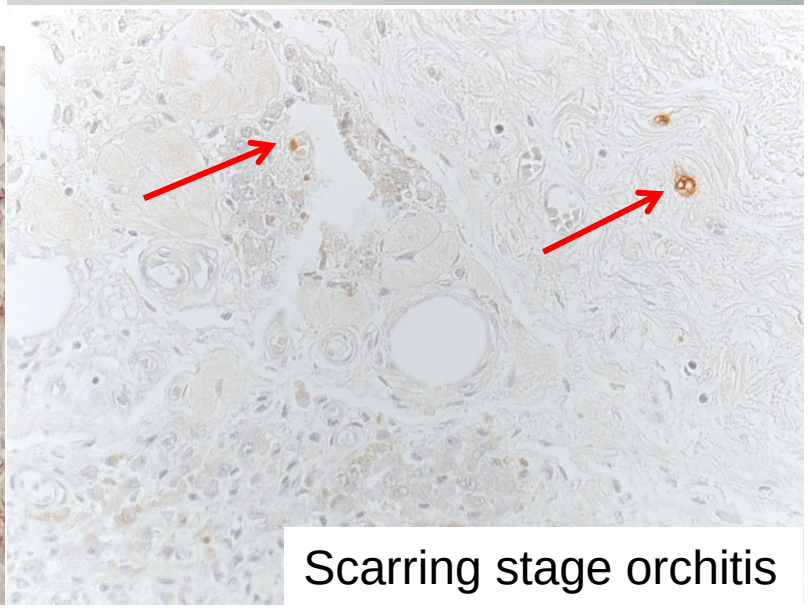


Central nerve lesions in Hansen’s disease (H&E and BCG immunostaining)



Active orchitis



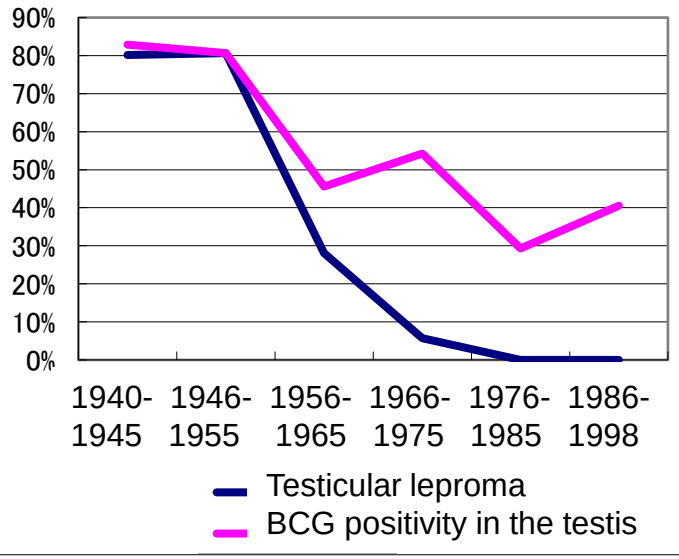


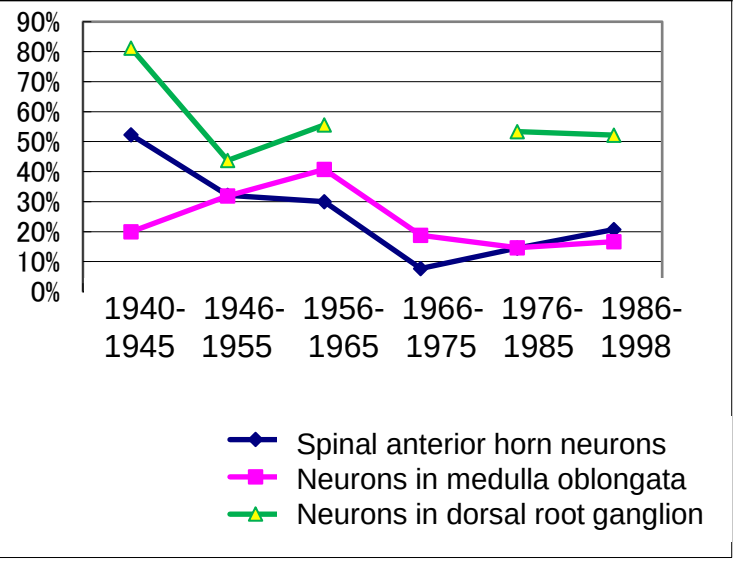
Scarring stage orchitis

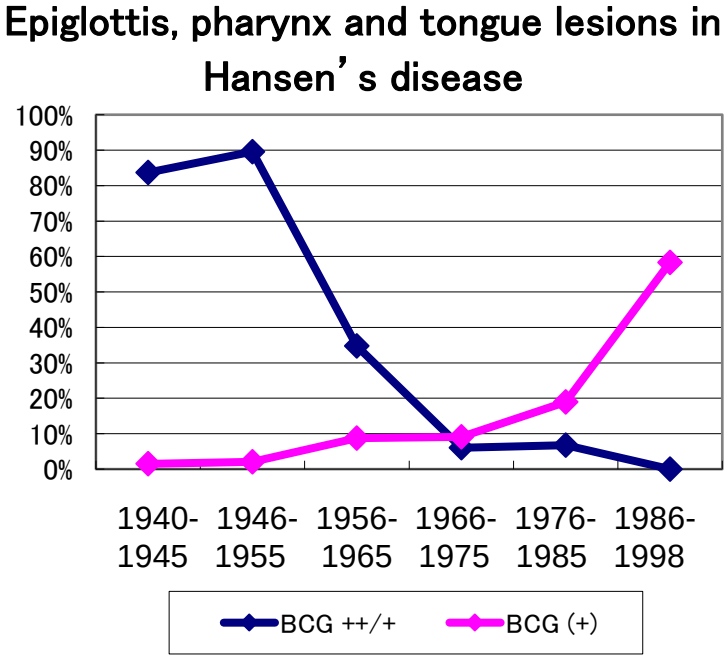
Lepromatous orchitis (active and scarring stages, lower panels: BCG immunostaining). In the scarring stage (right bottom), a few *Mycobacteria* are detected in macrophages.

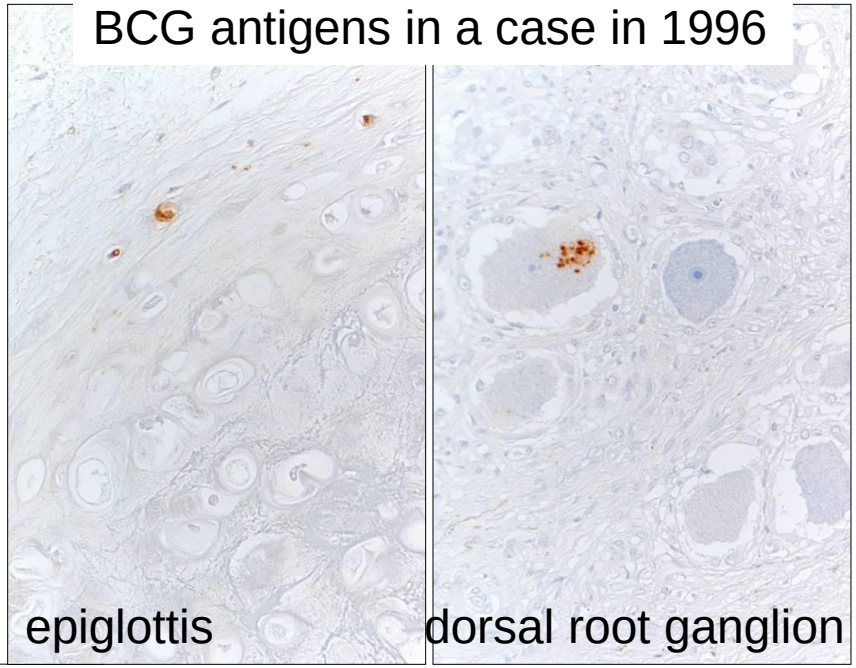
Laryngeal deformity by lepromatous lesions. Laryngeal stenosis can be a cause of death in Hansen's disease.

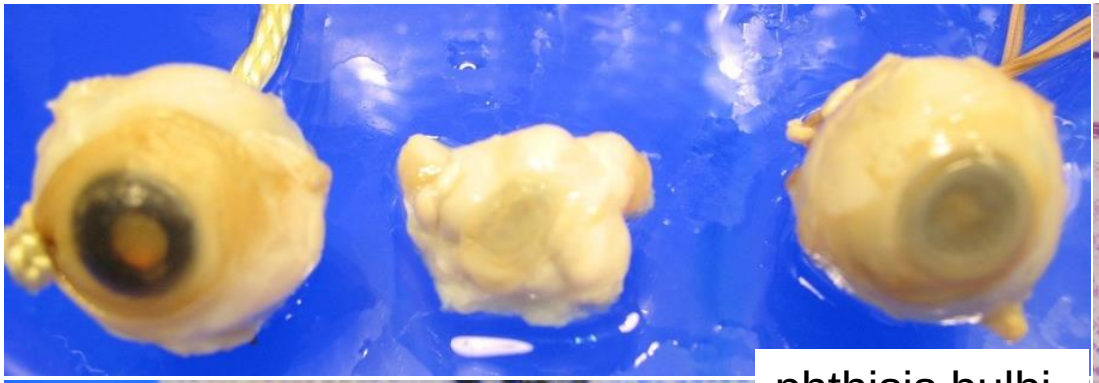
Lesions of the testis, central nervous system and pharynx/larynx in Hansen's disease



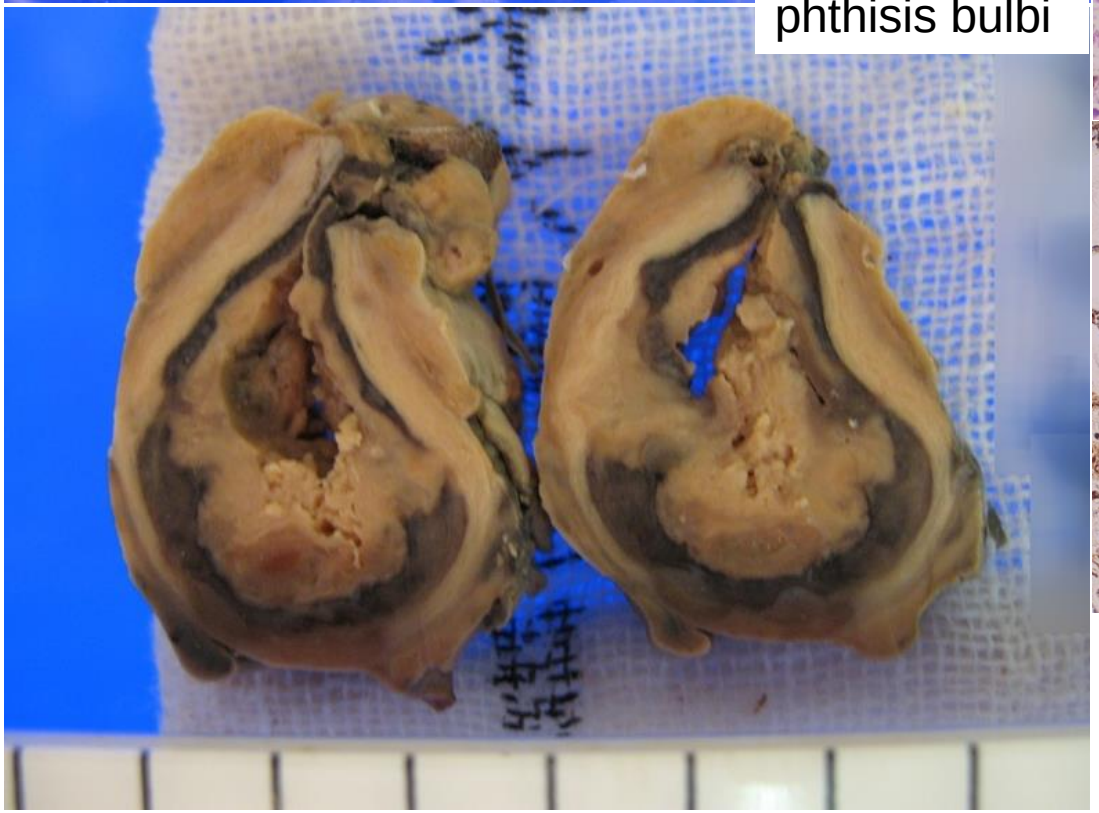


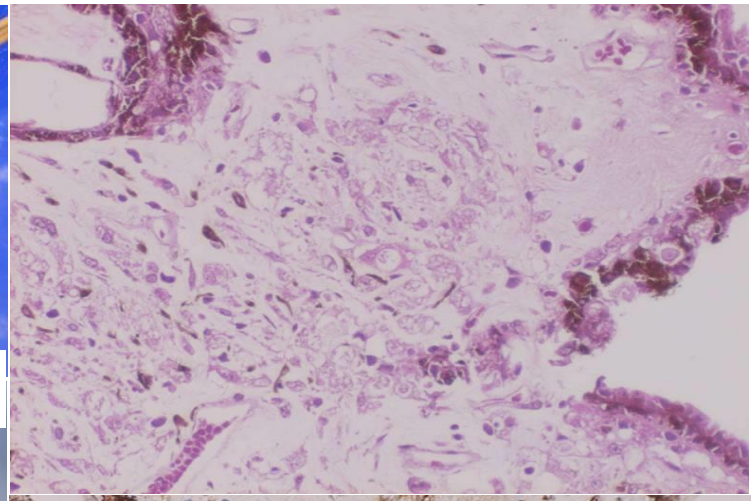


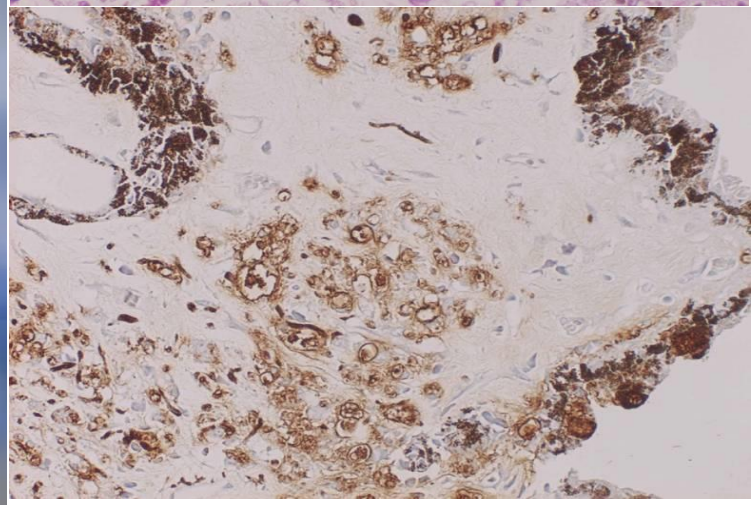




phthisis bulbi

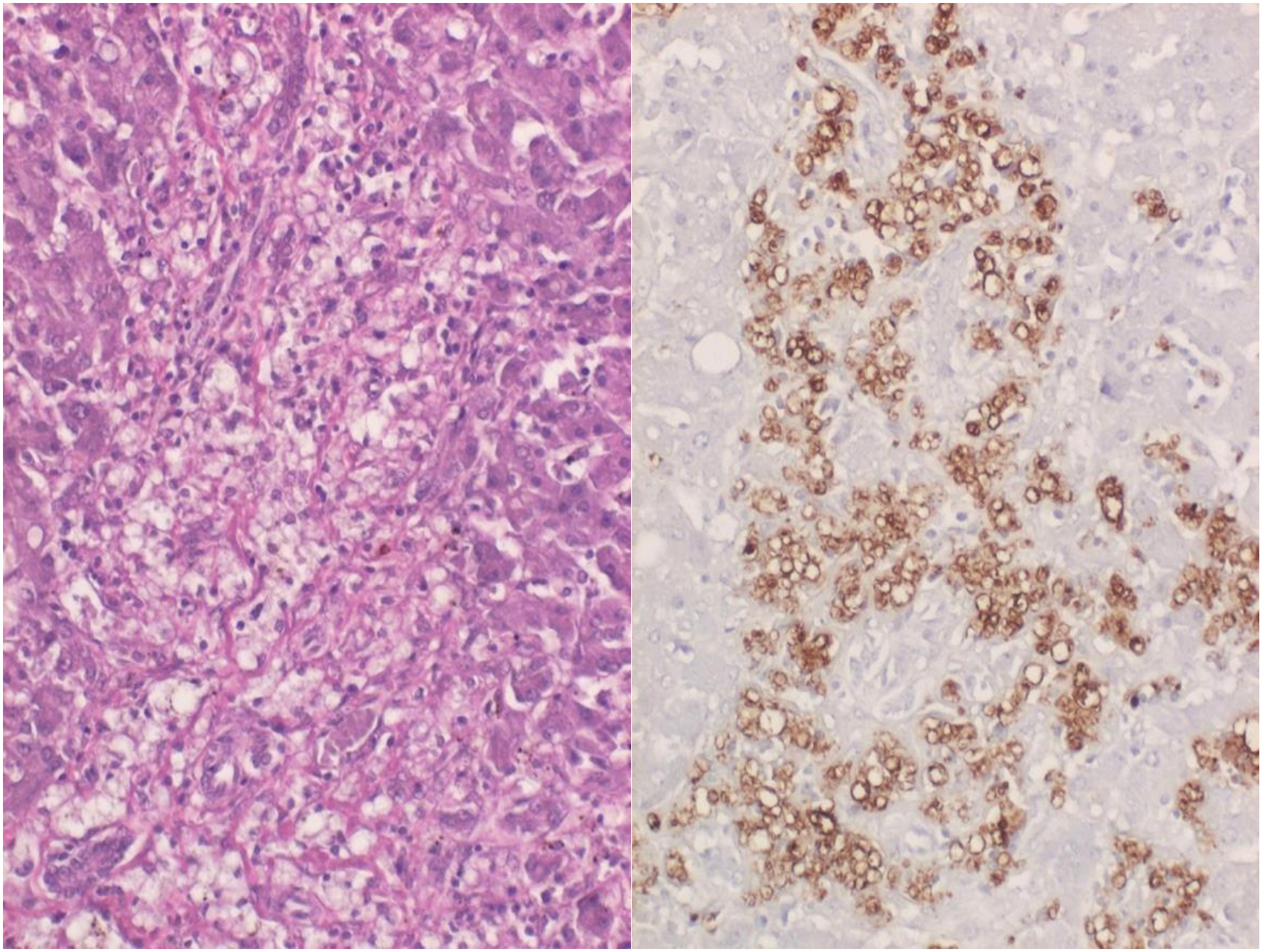






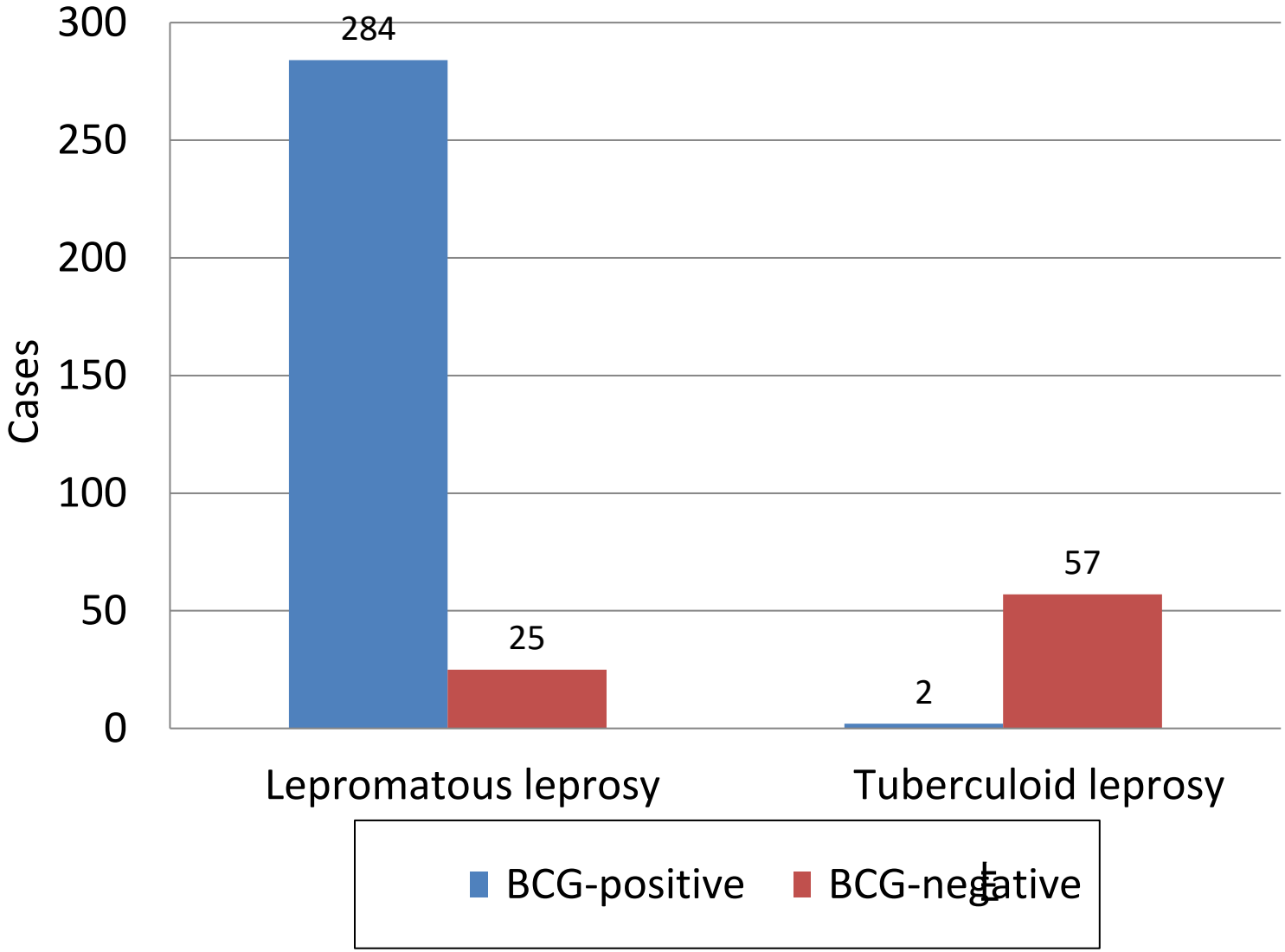
Lepromatous iridocyclitis
（top: H&E, bottom: BCG immunostaining）

Eye lesions in Hansen’s disease（with a high rate of blindness: left: phthisis bulbi)

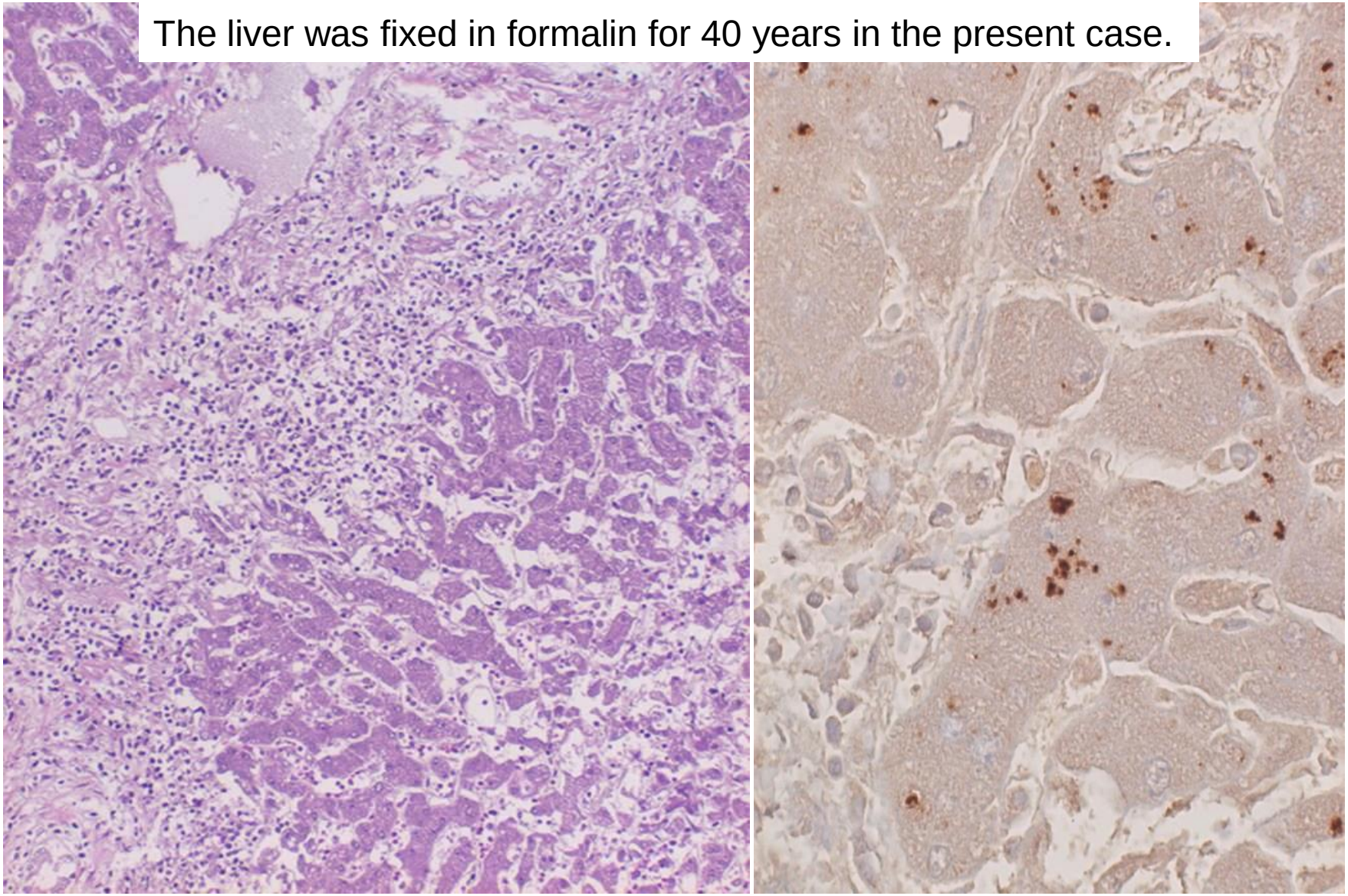


Lepromatous hepatitis (left: H&E: leproma, right: BCG immunostaining)

Two types of Hansen's disease and the lesions in internal organs (liver, spleen and adrenals) (judged by BCG immunostaining in cases of 1940-1950)

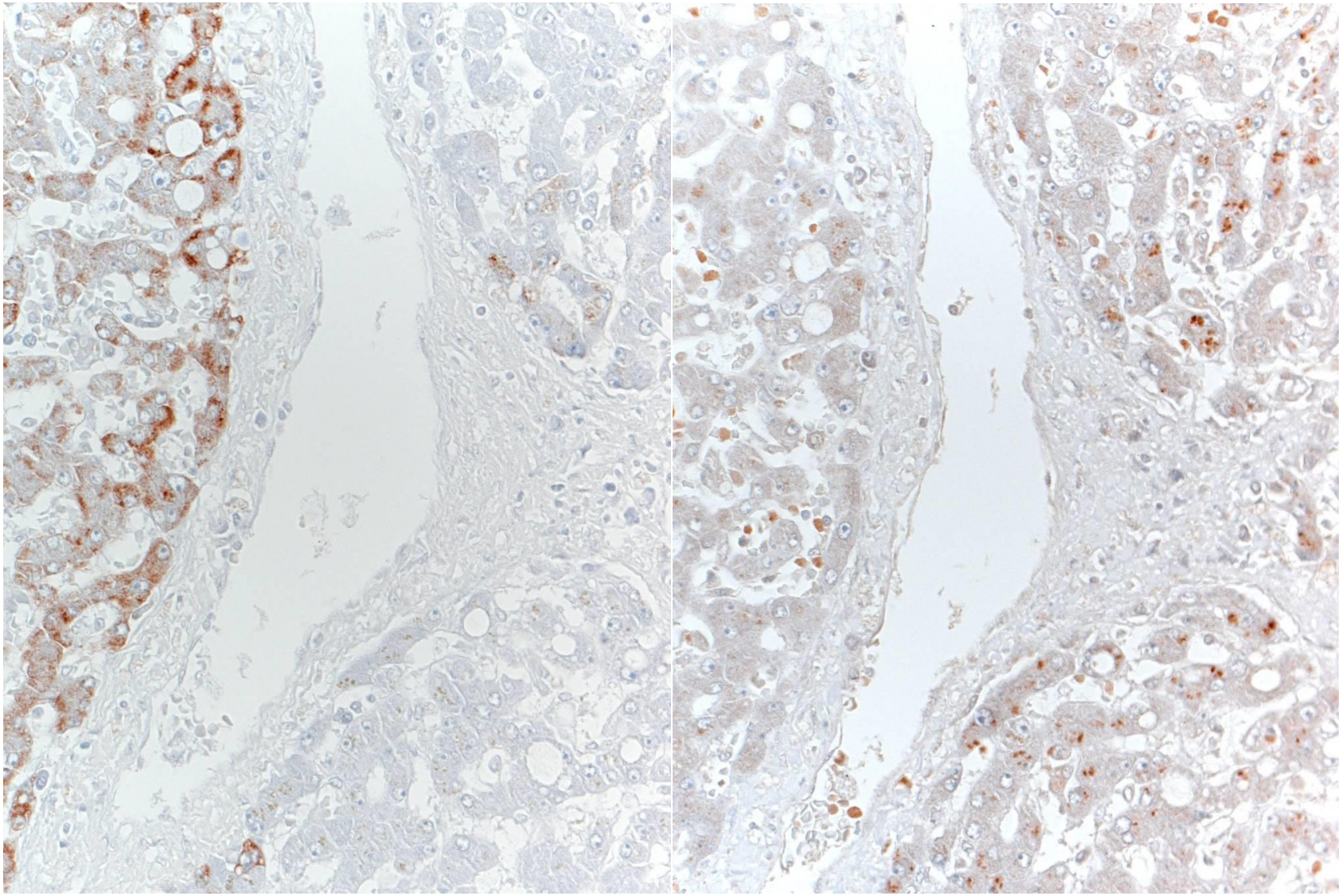


The liver was fixed in formalin for 40 years in the present case.



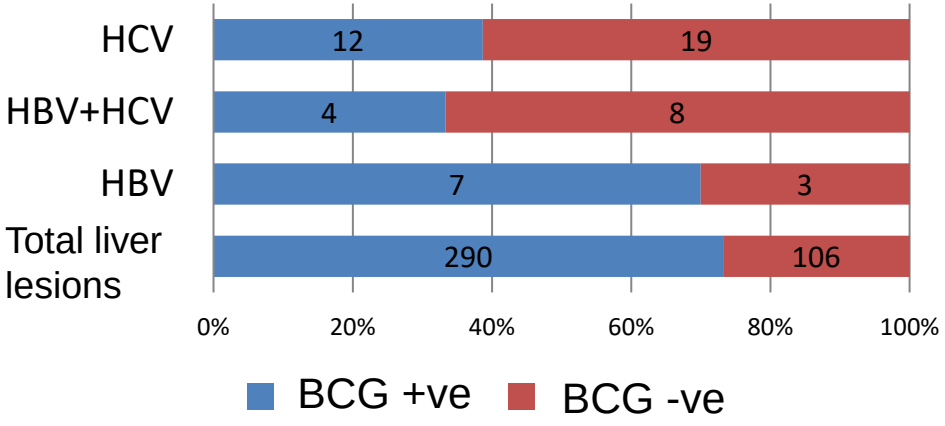
Chronic HCV hepatitis (left: H&E, right: immunostaining for HCV antigen)
Needles were shared for injecting Promin (a therapeutic medicine). The positivity rate of HCV was very high among patients with Hansen's disease.

Dual infection of HBV and HCV in the liver of Hansen's disease (an autopsy case in 1947)

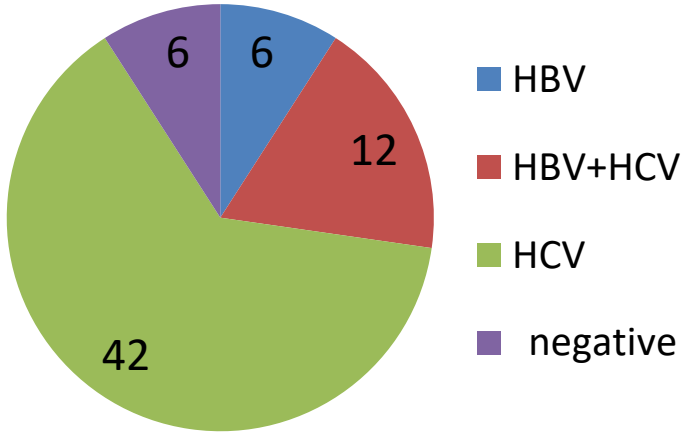


Immunostaining for HBs antigen (left: after proteinase K treatment) and HCV antigen (right: after heating treatment) in consecutive sections

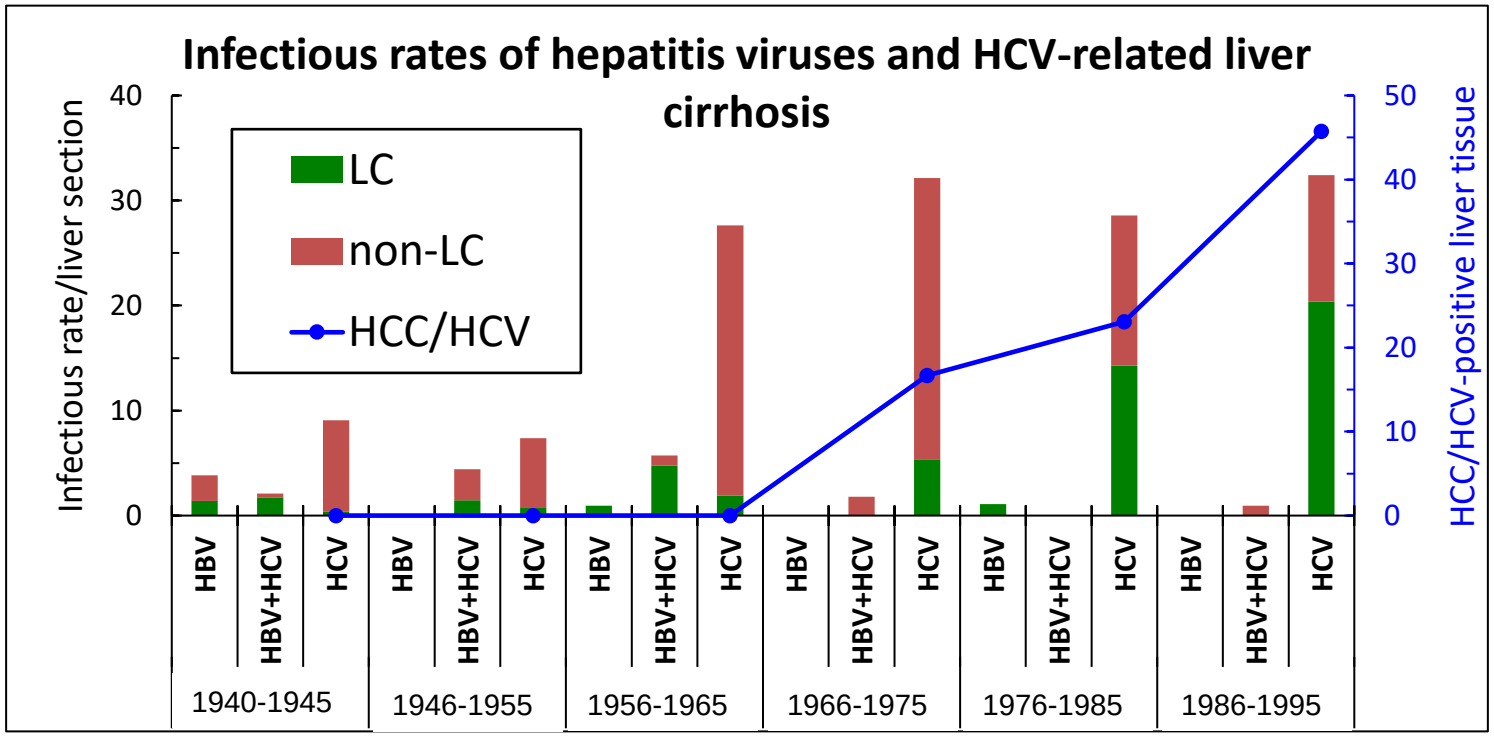
Lepromatous hepatitis and hepatitis viruses in 1940-1950



Liver cirrhosis and hepatitis viruses (n=66)

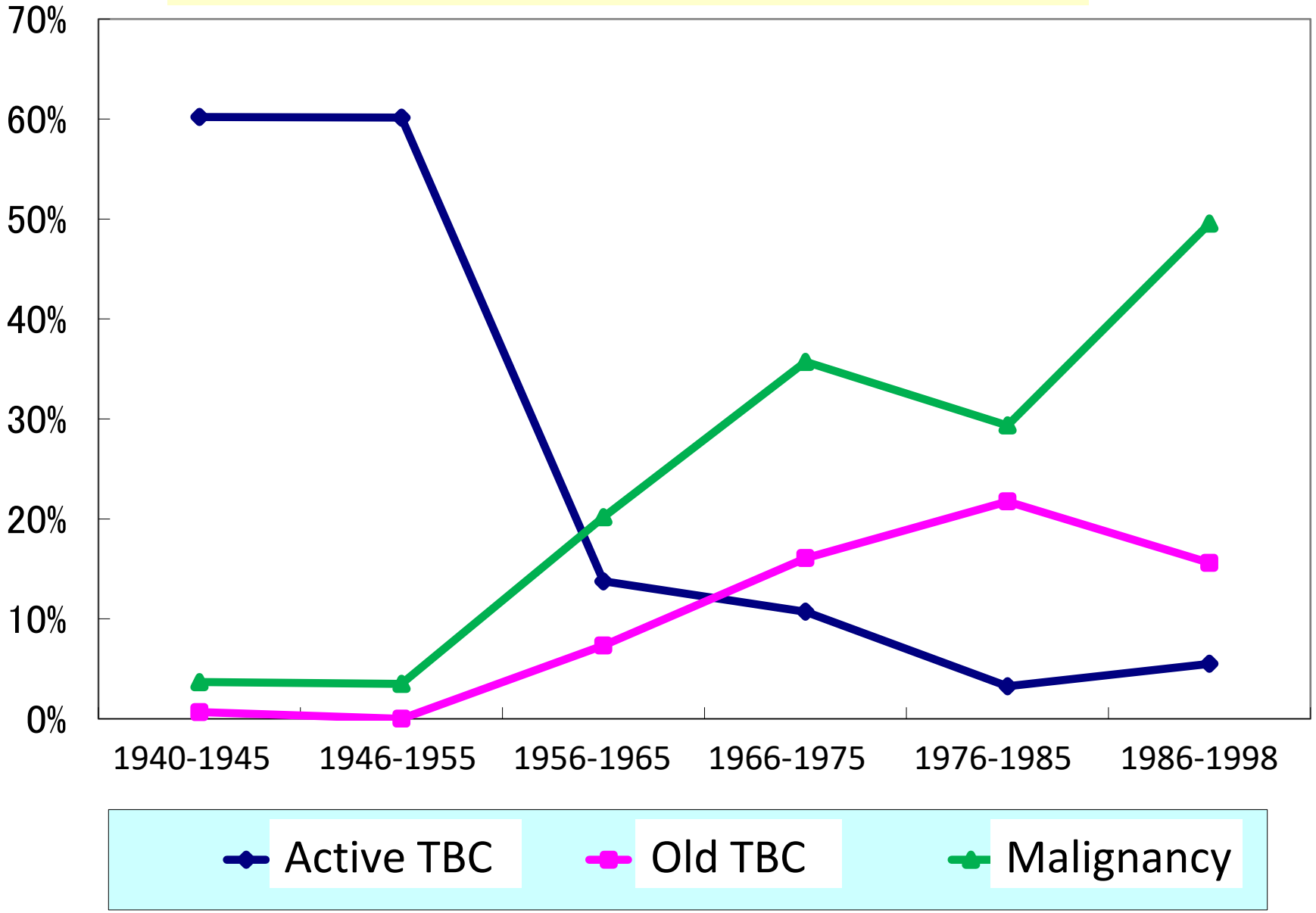


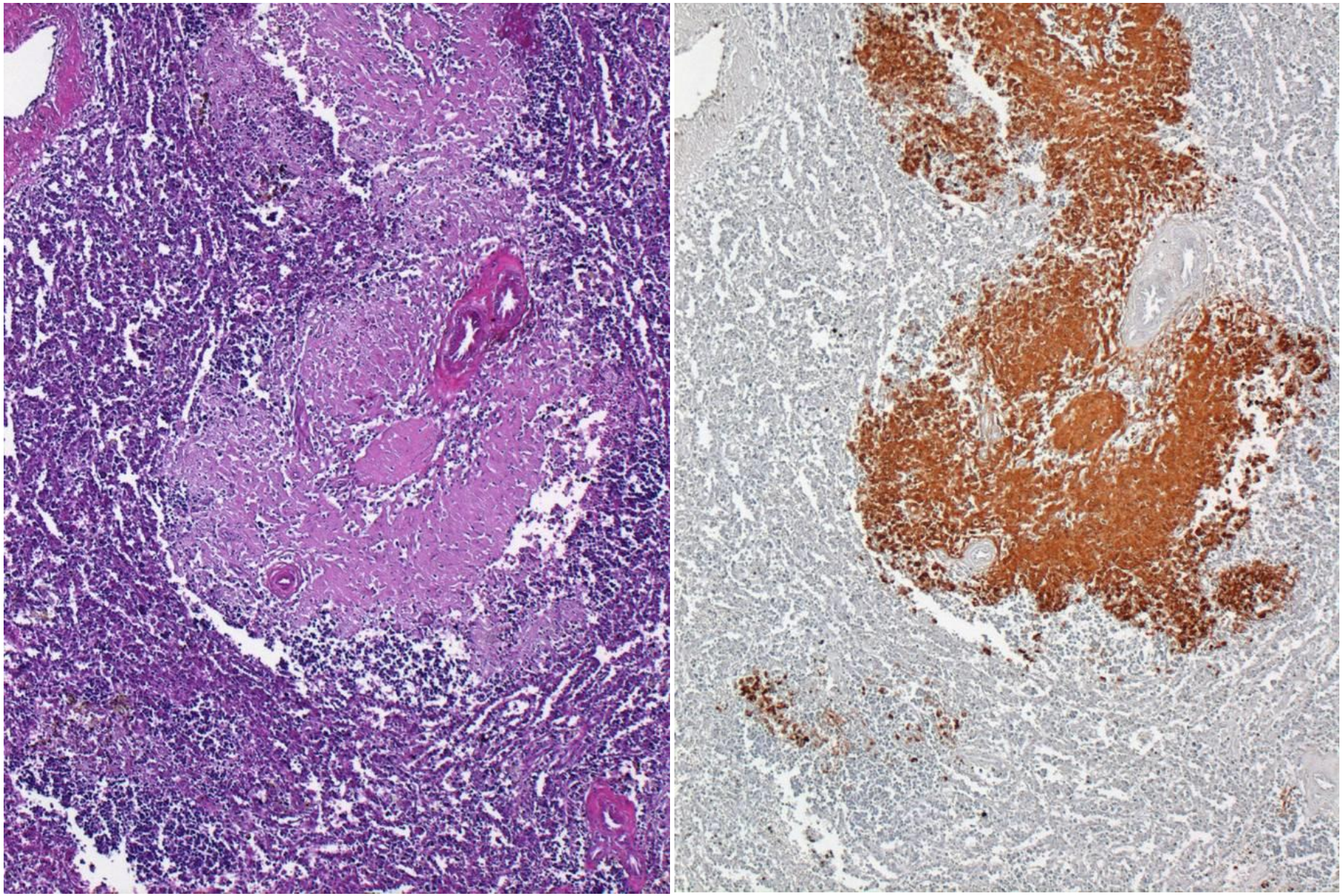
Infectious rates of hepatitis viruses and HCV-related liver cirrhosis



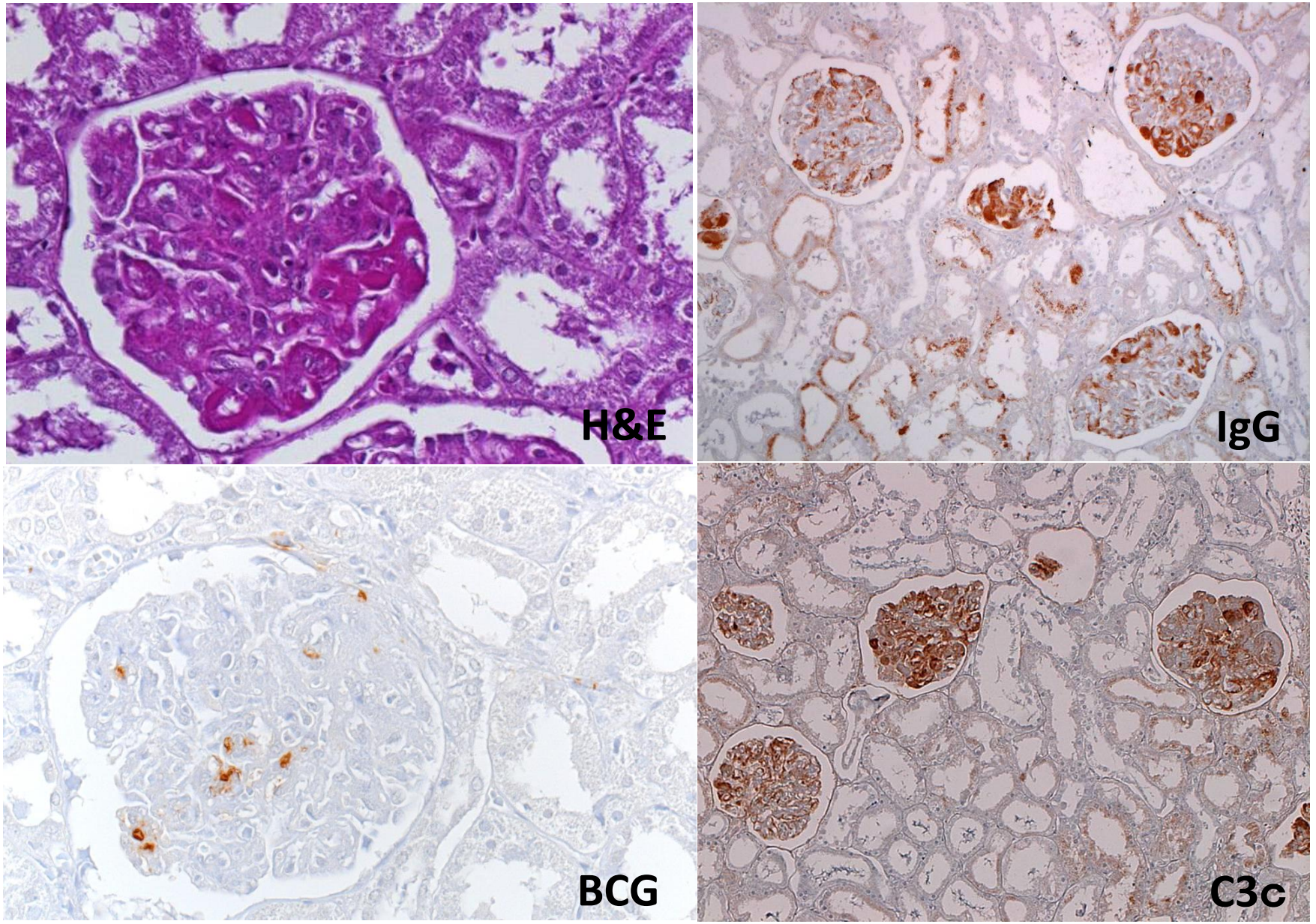
Lung tuberculosis with huge cavity formation (left) and intestinal tuberculosis with circular ulceration (right)

Tuberculosis and malignant neoplasms in Hansen's disease



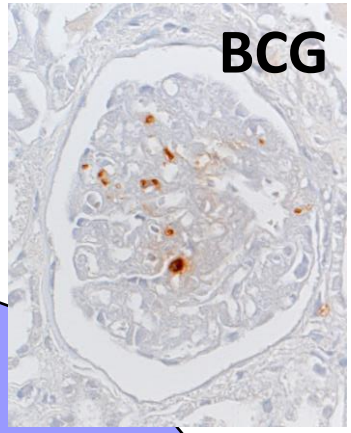


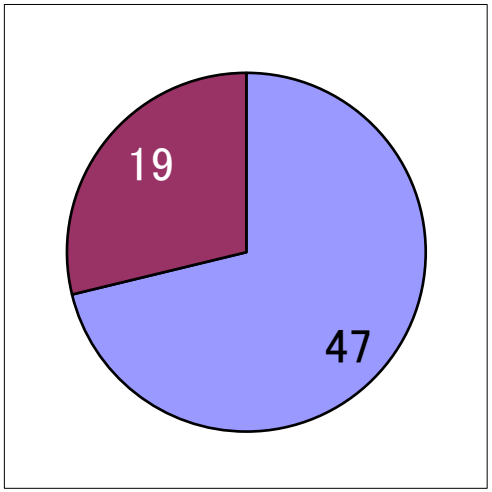
Secondary systemic amyloidosis (sago spleen) (left: H&E,
right: immunostaining for amyloid A protein)



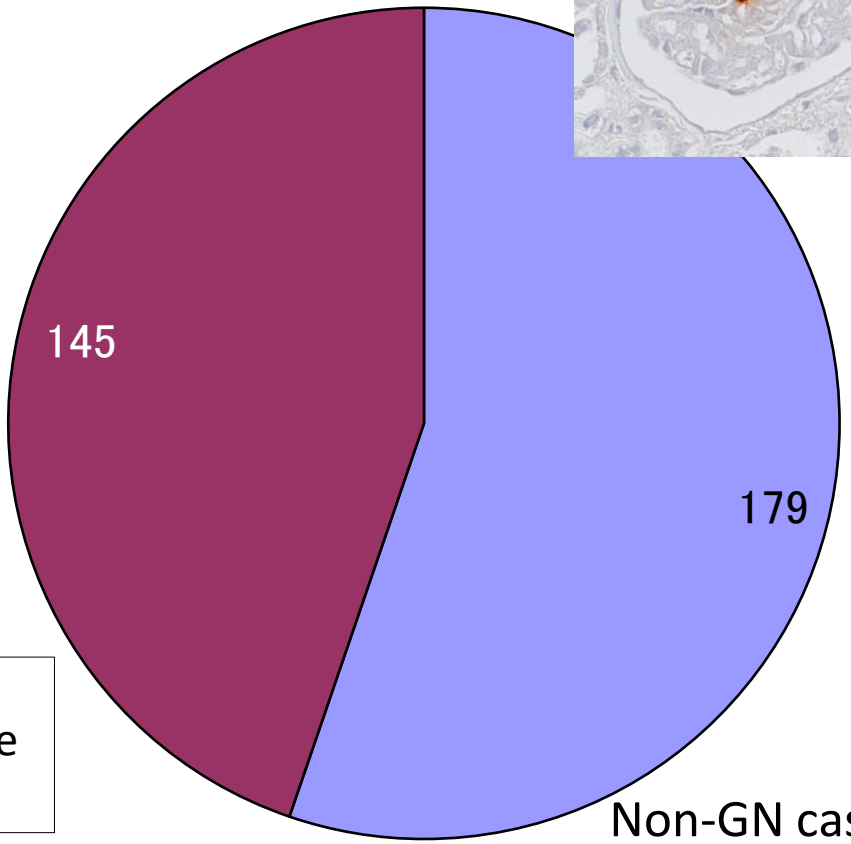
Chronic glomerulonephritis with wireloop-like immune deposition of IgG and C3c and BCG immunostaining (Mycobacterial antigen-positive)

Detection rates of glomerular BCG antigen in cases of glomerulonephritis (n=66) and non-GN (n=324) in 1940-1950





Cases with glomerulonephritis

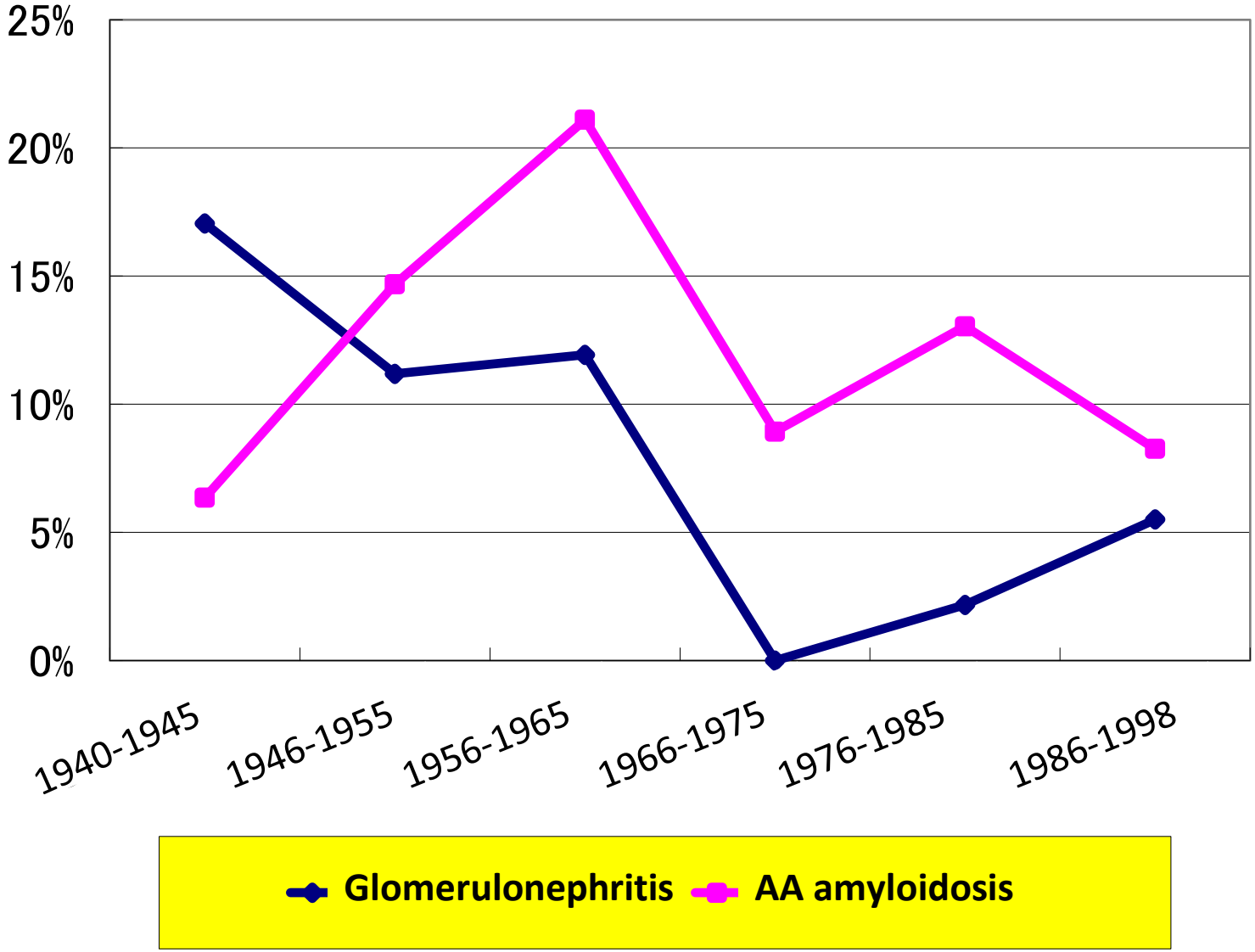


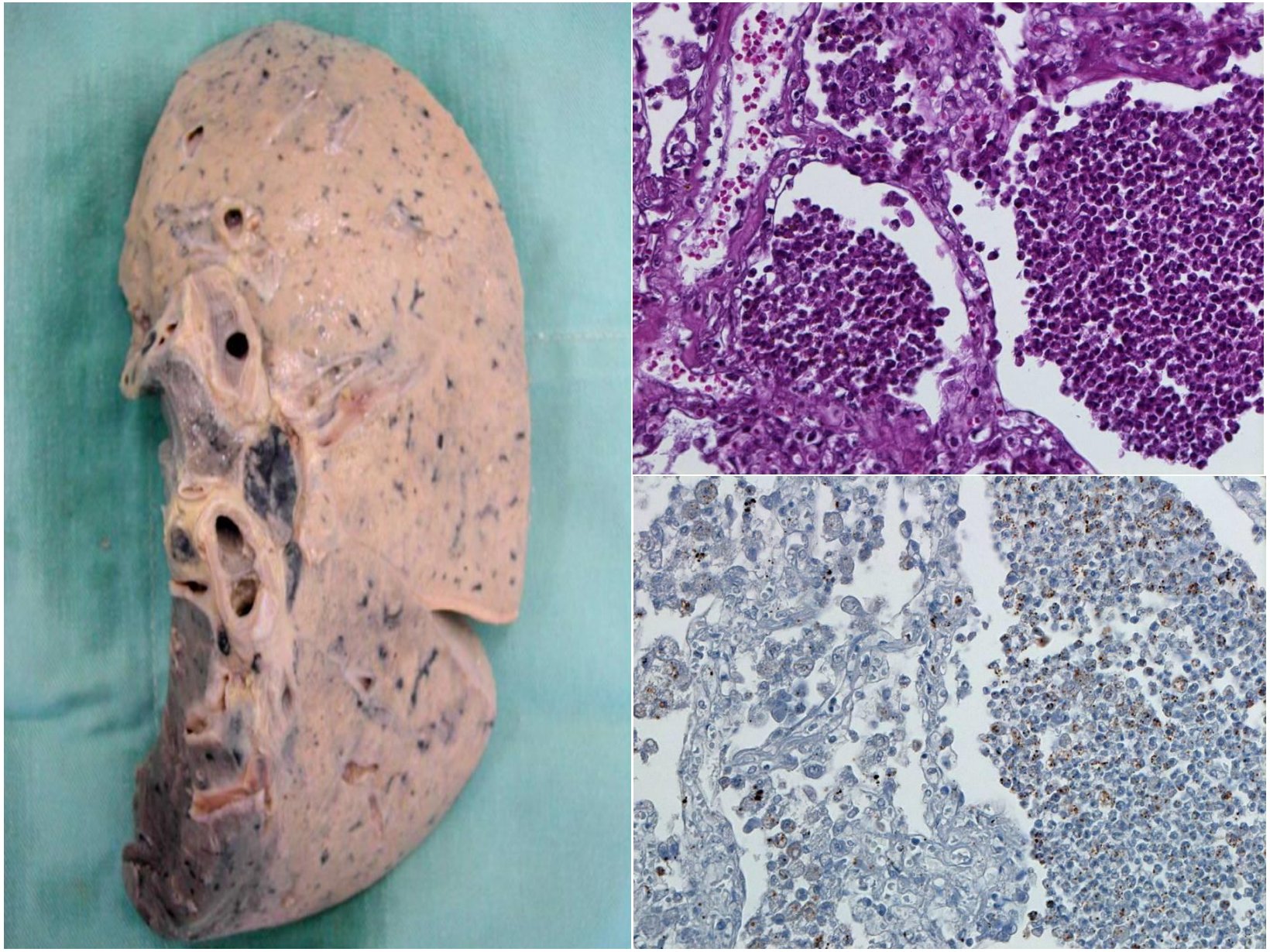
Non-GN cases

BCG-positive BCG-negative

In cases with glomerulonephritis, the rate of BCG antigen detection in the glomeruli is high ($p<0.01$).

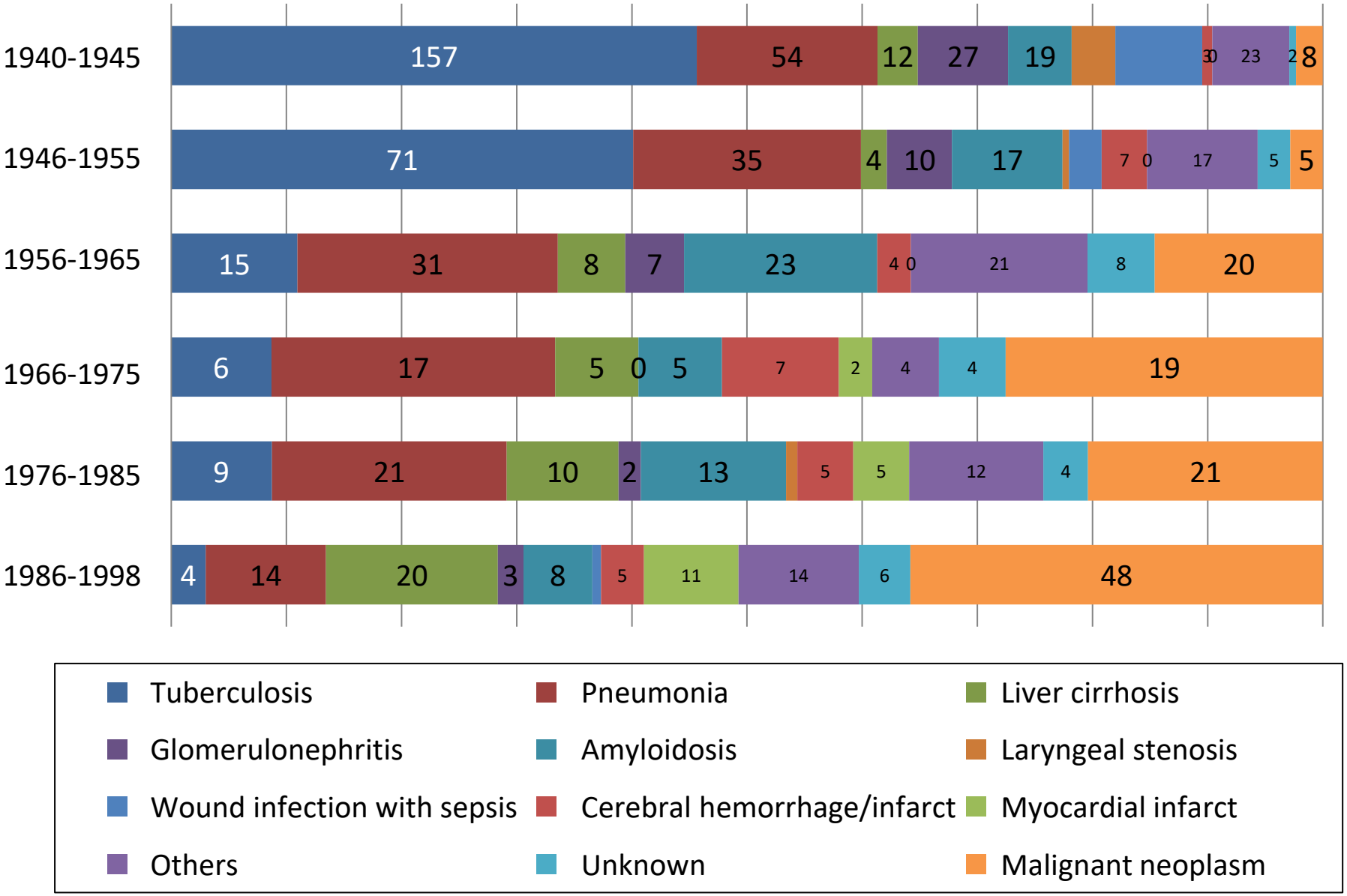
Secondary AA amyloidosis and glomerulonephritis in Hansen's disease





Pneumococcal lobar pneumonia (left: gross appearance, right top: H&E, right bottom: immunostaining for pneumococcal antigens)

Cause of death in patients with Hansen's disease



Hansen's disease in Oku-Komyoen

1) In lepromatous leprosy, lepromas were commonly formed in the liver, spleen, lymph nodes and adrenals. Tiny BCG antigen-positive infectious foci were also observed in the kidney, lung and pancreas. In tuberculoid leprosy, the internal organs were scarcely involved.
2) In the testis, pharynx, larynx, peripheral nerves and central nervous system, BCG antigen immunoreactivity was often observed in cases autopsied in 1980's and 1990's.
3) Leproma-related laryngeal stenosis and septicemia caused by wound infection were seen in cases during the World War II (1940-1945).
4) Active tuberculosis was the main cause of death of patients with Hansen's disease until 1955.
5) Death by malignancy increased after 1965.
6) Pneumonia was the significant cause of death throughout the entire period (lobar pneumonia until 1955 and bronchopneumonia after 1956).
7) Dual infection of HBV and HCV was common until 1954, and HCV infection increased after 1955 (caused by shared needles for injecting Promin). HCV-related liver cirrhosis followed and the complication of hepatocellular carcinoma (HCC) increased after 1985.
8) The incidence of glomerulonephritis and secondary systemic AA amyloidosis was unexpectedly high. Glomerulonephritis was common during the World War II, and secondary amyloidosis was peaked in 1956-1965.