

AIMS

1. To learn about the four different types of hypersensitivity reaction.
2. To understand that hypersensitivity reactions are the result of the immune system causing disease.
3. To explore nasal polyps, Hashimoto's thyroiditis, glomerulonephritis in the kidney and tuberculosis as examples of hypersensitivity reactions.

INTRODUCTION

Immune responses enable humans and animals to live in a world occupied by potentially damaging chemicals and organisms. However, sometimes the immune response itself may cause disease. This may occur in a number of ways, and we call these various reactions

HYPERSENSITIVITY REACTIONS.

Hypersensitivity reactions can be classified on the basis of the type of immune mechanism that causes the disease (see table below):

Hypersensitivity Type	Mechanism	Examples
I Anaphylactic type	Allergen (antigen) binds to IgE on mast cells which causes degranulation with the release of chemotactic, vasoactive and spasmogenic mediators.	Nasal polyps Asthma Hay fever
II Cytotoxic type	Antigen (endogenous or exogenous) on cell surface is bound by IgG or IgM causing cell dysfunction or cell destruction by phagocytosis or cell lysis.	Hashimoto's thyroiditis Acute rheumatic fever
III Immune complex type	Free-floating antigen is bound by IgG, IgM and IgA forming immune complexes which deposit in various tissues and activate complement initiating an acute inflammatory reaction (local or systemic).	Systemic Lupus Erythematosus Some types of glomerulonephritis
IV Delayed type (or Cell-mediated type)	Antigen is presented by antigen presenting cells and recognised by sensitised T-cells which recruit macrophages which may form granulomas (in the case of CD4+ T-cells) or kill cells directly (in the case of CD8+ T-cells /CTLs)	Tuberculosis Contact dermatitis Transplant rejection

TYPE I – e.g. nasal polyp

9.1 Polyp (H&E)

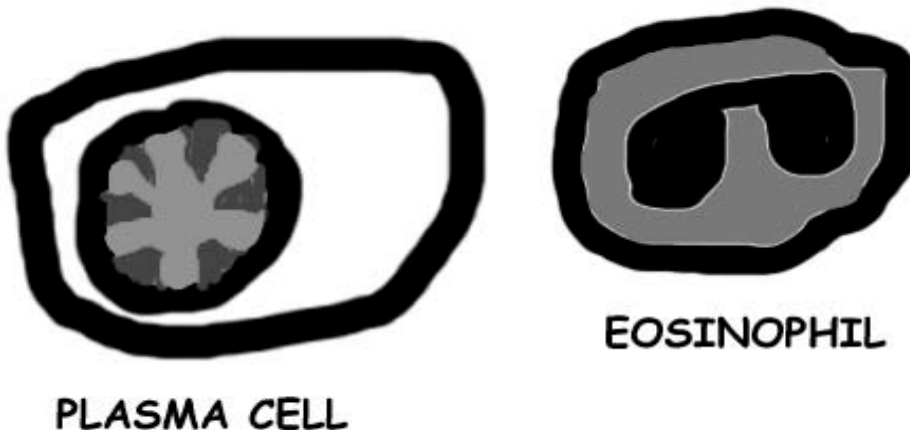
9.2 Polyp (Toluidine blue) 89.758 & 04.17c

Catalogue Number	Small Image	Image Map	Large Image
A_NP_PQ_NO_07.jpg	Nasal polyp		Nasal polyp
A_NP_PQ_NO_04.jpg	Nasal polyp		Nasal polyp
A_NP_PQ_NO_05.jpg	Nasal polyp	Image map	Nasal polyp
A_NP_PQ_NO_06.jpg	Nasal polyp (toluidine blue)	Image map	Nasal polyp (toluidine blue)

A polyp is a growth protruding from the mucous lining of an organ such as the nose (or bladder, or intestine), often causing obstruction. Some polyps are due to hypersensitivity type I reactions such as this nasal polyp, whereas others may be inflammatory (non-hypersensitivity) in origin.

Look first at the H&E section and identify the following features:

- i) respiratory epithelium (lining outside surface of polyp)
- ii) small blood vessels
- iii) oedema fluid in tissue spaces (seen as apparently empty spaces in this section).
- iv) inflammatory cells in the tissue spaces - plasma cells (eccentric, clock-face nuclei and dusky purple cytoplasm), eosinophils (bilobed nuclei and pink/red granular cytoplasm – look like a sunburnt face with sunglasses), lymphocytes (dark, single round nuclei and inconspicuous cytoplasm)



Now look at the toluidine blue section. Many details are shown less well than in the H&E section, but one feature is conspicuous: there are scattered cells with prominent purple granules in their cytoplasm. These are mast cells. These are difficult to identify in the H&E section.

Be sure you can answer these questions about the nasal polyp:

- Q1. Where are the IgE antibodies located?
- Q2. What is the likely allergen (antigen)?
- Q3. How does the oedema fluid develop?
- Q4. Give examples of the chemotactic and vasoactive mediators that are released?

Q5. What would you expect the symptoms to be? (On the basis of what you see, or perhaps your own experience or that of a colleague who may have Hay Fever.)

An alternative example of type I hypersensitivity is asthma – a **scanned image** can be viewed on computer: **Lung – bronchial asthma: 83.41**. Can you see increased eosinophils in the bronchial wall with thickening of the bronchial wall?

TYPE II – e.g. Hashimoto’s thyroiditis

**NE6 Normal thyroid
58.5**

Catalogue Number	Small Image	Image Map	Large Image
N_NE_TH_07.jpg	Normal thyroid		Normal thyroid
N_NE_TH_02.jpg	Normal thyroid		Normal thyroid

Normal thyroid is composed of groups of acini (or follicles); you can think of their appearance in three dimensions as a collection of bubbles. The follicles or acini are lined by thyroid epithelial cells and filled with colloid, a pink-staining proteinacious material (containing thyroglobulin), from which tri-iodothyronine (T3) and thyroxine (T4) are made. The acini are packed close together and vary in size. Intensely stimulated thyroid tends not to accumulate much colloid at all and the original central spaces become a tiny proportion of the total acinus, but the epithelial cells are tall.

**9.3 Hashimoto’s thyroiditis
58.356 & 66.117**

Catalogue Number	Small Image	Image Map	Large Image
A_AL_HU_TH_07.jpg	Hashimoto’s disease		Hashimoto’s disease
A_AL_HU_TH_04.jpg	Hashimoto’s disease	Image map	Hashimoto’s disease
A_AL_HU_TH_05.jpg	Hashimoto’s disease	Image map	Hashimoto’s disease

The acini or follicles have small central lumina with little colloid and the thyroid epithelium is tall. The stroma has been colonised by very large numbers of lymphocytes and plasma cells. This is a violent auto-immune reaction. Try to answer the following from the examination of the section:

- Q6. Is there evidence of tissue destruction? Is it a cytotoxic process?
- Q7. What type of T lymphocytes would you expect to be involved?
- Q8. Is the lymphoid infiltrate organised into lymphoid follicles with germinal centres?
- Q9. What is the mature cell produced by lymphoid follicles with germinal centres? Can you see many examples of this mature cell in the section? What is its effect on thyroid epithelium?
- Q10. What is likely to be the effect of these changes on plasma levels of thyroxine and tri-iodothyronine? Why do the remaining thyroid acini (or thyroid follicles) have an “over-stimulated” appearance with little colloid and tall epithelium?

TYPE III – e.g. Systemic Lupus Erythematosus

A scanned image of an example of type III hypersensitivity can be viewed on computer: **Kidney glomerulonephritis: 49.464**. Can you see changes (increased cells) in the glomeruli? What are these extra cells?

Think about the following questions regarding type III hypersensitivity in relation to Systemic Lupus Erythematosus (SLE), a disease process in which auto-antibodies are made against DNA or other chromatin components. SLE patients often have skin rashes due to inflammation of blood vessels (vasculitis) in the skin, kidney disease due to inflammation of the glomeruli (glomerulonephritis), and joint disease due to inflammation of the synovium (arthritis). Type III hypersensitivity is caused by immune complexes being deposited.

Q11. What makes up an 'immune complex'?

Q12. Where (in which structures) are immune complexes deposited?

Q13. How do deposited immune complexes trigger an inflammatory response?

TYPE IV – e.g. Tuberculosis

An important cause of granulomatous inflammation is infection by **Mycobacteria**. These long-lived bacteria proliferate slowly but are protected by their thick, waxy outer coat. They initiate a type IV delayed type hypersensitivity response. They are difficult for phagocytes to kill, and although initially a few neutrophils may be involved, very soon macrophages with surviving **intracellular bacteria** dominate the response.

Initial (primary) infection is usually in the lungs, (but it may be in tonsil or Peyer's patches of the small intestine with other types of mycobacteria). Alveolar macrophages ingest the bacteria and some enter the interstitium to be carried by the lymph to the draining lymph nodes, usually at the hilum. In the lymph nodes the bacterial antigens are presented, generating a cell mediated immune response dominated by CD4+ T lymphocytes known as Th1 cells. These Th1 cells release cytokines, including IFN- γ , that can recruit and activate macrophages.

Initially, the response is at **two separate sites**; one is the site of entry, usually the periphery of the lung (which is called the **Ghon focus**) and the other is within the draining lymph nodes. This pattern is known as the **primary complex** (Ghon focus + local lymph node involvement).

In the lymph node, the response is dominated by **Th1/macrophage** co-operation (leading to macrophages aggregating to form granulomas) and as soon as any T cells, which have been sensitized in the lymph node, reach the Ghon focus via the bloodstream, granulomas develop there as well. The macrophages in granulomas usually become activated (enlarged with much pink cytoplasm – called "epithelioid" macrophages because they resemble epithelial cells in the large amount of cytoplasm they have), allowing them to secrete more enzymes with greater killing ability. Some macrophages fuse together to form "giant cells" with many nuclei (often forming a ring or U shape in one large cytoplasmic mass) – sometimes called a 'Langhans' cell. In most individuals the bacteria are eventually killed and both sites of the primary complex heal by fibrosis, often followed by calcification.

However, sometimes, especially in children, the infection **persists**; more and more macrophages accumulate and die. These macrophages release enzymes. There is formation of soft dead material resembling **cream cheese** (caseous necrosis), due to destruction of normal tissues by released enzymes. At the same time, the mechanisms of healing are activated and fibroblasts lay down collagen. This state of 'cheesy' tissue destruction surrounded by attempted healing is **fibro-caseous tuberculosis**.

Hilar lymph nodes may enlarge and the destructive process may reach a thin walled pulmonary vein, which allows the soft crumbly material with clumps of infected macrophages to enter the blood and be distributed around the whole body. Where each tiny clump lodges, the same process is

repeated. The lymphocytes and macrophages gather, producing granulomata, which reach a size where they are visible to the naked eye.

This blood spread allows infection to reach the meninges and granulomatous inflammation spreads over the surface of the brain (**tuberculous meningitis**). Even with treatment, the patient is likely to die at this stage, and in ancient times, physicians saw tiny white round bodies looking like millet seed (miliary) distributed throughout the body after death. This appearance has given rise to the term **miliary tuberculosis**.

Other outcomes than **recovery or early death** occur. Sometimes a chronic state is established, because of inability of the immune system to eradicate the bacilli. *Mycobacterium tuberculosis* itself is not very destructive and yet terrible tissue destruction takes place as the body's own cells are recruited and themselves die. This process represents **TYPE IV HYPERSENSITIVITY**.

CHRONIC TUBERCULOSIS (Post-primary TB or Secondary TB) most often occurs in the lungs and it is difficult to know if it is **persistent** from the first infection (perhaps even being **reactivated** many years later) or whether there has been true **re-infection**. Chronic infection also occurs at other sites as a result of blood spread, which lead not to miliary tuberculosis but to persistence in certain favourable environments.

Since many years may elapse before infection at these distant sites is recognized, it suggests that sometimes mycobacteria may be held in check and when the immune system becomes less effective, (due to age, immunosuppression, malnutrition, other disease, etc), the disease progresses once again.

The response to *M. tuberculosis* illustrates how the immune system can **modify the course of an infectious disease**. On **first exposure**, there is **rapid spread** from the portal of entry to the lymph nodes. On **re-exposure**, the circulating long-lived lymphocytes with "memory" of the antigens immediately recruit other lymphocytes to immobilise and stimulate macrophages with ingested organisms. This means that re-infection may be **localised to the site of entry**.

Mycobacteria have a cell wall which contains a wax-like substance, mycolic acid. This does not take up the stains generally used for tissue and bacteria, so in order to reveal them, the **ZIEHL-NEELSEN STAIN** is used. The specimen is exposed to a **hot solution** of basic dye (carbol-fuchsin) which is able to penetrate the wax. The binding of the dye is so strong that subsequent treatment with solvents such as acid and alcohol does not remove it.

Mycobacteria which cause tuberculosis are often termed **acid & alcohol-fast bacilli** (or AAFB). Some other types of Mycobacteria are acid-fast only.

Catalogue Number	Small Image	Image Map	Large Image
M_BI_MB_10.jpg	BCG growth on Lowenstein-Jensen		BCG growth on Lowenstein-Jensen
M_BI_MB_02.jpg	Ziehl-Neelsen stained sputum		Ziehl-Neelsen stained sputum

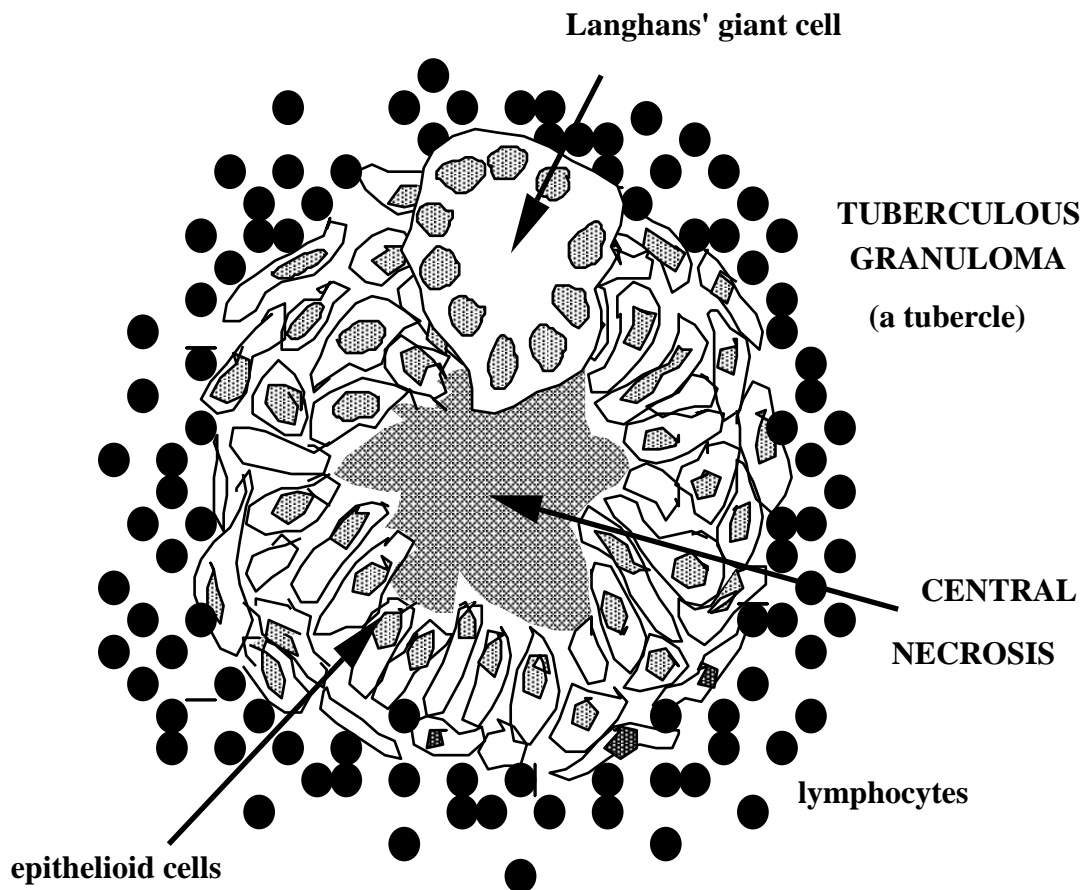
9.4 Lymph node: tuberculosis 73.1120

Scanned images on computer can also be viewed: Lymph Node: TB 66.0255 or 80.0281

Catalogue Number	Small Image	Image Map	Large Image
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A_TB_GN_LN_19.jpg	Tuberculosis		Tuberculosis
A_TB_GN_LN_11.jpg	Tuberculosis		Tuberculosis
A_TB_GN_LN_04.jpg	Tuberculosis	Image map	Tuberculosis
A_TB_GN_LN_12.jpg	Tuberculosis		Tuberculosis

Note granulomata at different stages, some with and some without central necrosis. As tuberculous granulomata enlarge they coalesce, giving rise to larger areas of necrosis. The bacteria are not visible with this stain.



Miliary Tuberculosis

9.5 Lung: miliary tuberculosis 55:274

Catalogue Number	Small Image	Image Map	Large Image
A_TB_ML_LU_07.jpg	Miliary tuberculosis		Miliary tuberculosis
A_TB_ML_LU_04.jpg	Miliary tuberculosis	Image map	Miliary tuberculosis

From an eighteen-month old boy who died of miliary tuberculosis and subsequent tuberculous meningitis. The basic structure of the granulomata resulting from blood spread to the lung, is exactly like those you have seen in the lymph node, but they are widely separated from each other.

**9.6 Lung: miliary tuberculosis (Ziehl-Neelsen)
68.808**

Catalogue Number	Small Image	Image Map	Large Image
A_TB_ML_LU_06.jpg	Miliary tuberculosis (ZN)		Miliary tuberculosis (ZN)
A_TB_ML_LU_05.jpg	Miliary tuberculosis (ZN)		Miliary tuberculosis (ZN)

From an **immuno-suppressed** adult, who had received immune suppressing drugs following a renal transplant. A few of the granulomas contain large numbers of **red-staining M. tuberculosis**, visible with the x40 (high dry) objective. (There may be only one granuloma near the edge of your section containing numerous bacilli; ask a demonstrator if you cannot find any).

Post-Primary Tuberculosis

In adults, the commonest form of secondary (or post-primary) infection by *M. tuberculosis* affects the **apex of both lungs**. In otherwise healthy individuals, this usually heals, but in the debilitated or malnourished, the disease may spread.

**9.7 Lung : post-primary tuberculosis (H&E)
9.8 ditto (ZN)
57.110**

These are large sections, to be shared. Please be careful not to break them.

Scanned images on computer can also be viewed:

Lung: fibro-caseous TB 60.1158 or 50.0470

Lung: TB bronchopneumonia 57.0350

Catalogue Number	Small Image	Image Map	Large Image
A_TB_FS_LU_02.jpg	Post-primary tuberculosis		Post-primary tuberculosis
A_TB_FS_LU_03.jpg	Post-primary tuberculosis (ZN)		Post-primary tuberculosis (ZN)
A_TB_FS_LU_10.jpg	Post-primary tuberculosis		Post-primary tuberculosis
A_TB_FS_LU_11.jpg	Post-primary tuberculosis (ZN)		Post-primary tuberculosis (ZN)

From the right upper lobe of a lung which was removed from a woman who had been suffering from tuberculosis for seven years and was losing weight.

The cavitation is due to destruction of lung tissue with erosion of a bronchus. Infected necrotic tissue had been coughed up by the patient, with the obvious risk of infecting others and left this cavity in the lung.

Be sure you can answer these questions about the responses seen in tuberculosis:

- Q14. What makes mycobacteria different from other bacteria?
- Q15. In a case of lung infection by TB, where are the organism's antigens first presented to the immune system? How do the antigens get there?
- Q16. What sort of T cells are involved in the response?
- Q17. Why are HIV infected patients particularly susceptible to mycobacterial infection?
- Q18. What is a granuloma?
- Q19. What causes the tissue damage (caseation) in TB? Is it the virulence of the organism or the host immune response?

PROCESS IDENTIFICATION AND REPORT WRITING

9.9 Spleen: Unknown 55.274

Catalogue Number	Small Image	Image Map	Large Image
A_TB_ML_SP_01.jpg	Spleen : Unknown		Spleen : Unknown
A_TB_ML_SP_02.jpg	Spleen : Unknown		Spleen : Unknown
A_TB_ML_SP_03.jpg	Spleen : Unknown	Image map	Spleen : Unknown
A_TB_ML_SP_04.jpg	Spleen : Unknown		Spleen : Unknown

This is a block of spleen from a severely ill old person. Please draw a diagram, write a description and provide an interpretation with identification of the pathological process.

SOME WORDS USED

Granulum (Latin)	granule		
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- oma (Greek)	swelling	granuloma	
Tuber (Latin)		swelling	tubercle, tuberculosis
Milium (Latin)		millet-seed	miliary
Caseus (Latin)		cheese	cheesy

TIDYING UP

Before you leave, please remember to:
Dim and then switch off the microscope light.
Cover the microscope and leave it on the bench.
Return the wooden block if you used one.
Push the stool back.

Thank you!

DEMONSTRATION MUSEUM SPECIMENS

RABBITS injected with MYCOBACTERIA : differential susceptibility.

R 61.284

Catalogue Number	Small Image	Image Map	Large Image
A_EX_TB_VT_02.jpg	RABBITS injected with MYCOBACTERIA (Bovine)		RABBITS injected with MYCOBACTERIA (Bovine)

0.04 mgs of **BOVINE** *M. tuberculosis* given intravenously. It died four weeks later.
 Note numerous miliary lesions, especially in the lungs.

R 61.285

Catalogue Number	Small Image	Image Map	Large Image
A_EX_TB_VT_01.jpg	RABBITS injected with MYCOBACTERIA (Human)		RABBITS injected with MYCOBACTERIA (Human)

0.04 mgs of **HUMAN** *M. tuberculosis* given intravenously.
The animal was killed 5 weeks later. Miliary lesions but to a **lesser degree**.
Rabbits are **more susceptible** to **BOVINE** than to **HUMAN** *M. tuberculosis*.

GUINEA PIG : M. tuberculosis
R61.287

Catalogue Number	Small Image	Image Map	Large Image
A_EX_TB_VT_03.jpg	Guinea pig: M. tuberculosis		Guinea pig: M. tuberculosis

Intramuscular human *M. tuberculosis* was given into the right thigh and the animal killed 6 weeks later. Note the enlarged draining lymph nodes, scattered lesions in the lungs, liver and spleen. Much of the pallor of the liver is due to fatty change. The lesions resemble a human **primary complex** with **miliary spread**.

CLASS 9 MUSEUM SPECIMENS

I **LUNG: PRIMARY COMPLEX & MILIARY SPREAD** **P47.088**

Catalogue Number	Small Image	Image Map	Large Image
A_TB_ML_LU_10.jpg	Lung: Primary complex & miliary spread		Lung: Primary complex & miliary spread

An 11 year old girl had a three week history of persistent vomiting. On admission there were signs of meningitis and tubercle bacilli were found in the cerebro-spinal fluid. She died eight days later and was found to have miliary tuberculosis with meningitis.

In the lung there is a peripheral yellow nodule (**GHON FOCUS** - the site of primary infection) and enlarged hilar lymph nodes, which together constitute the **PRIMARY COMPLEX**. The tiny yellow tubercles seen in other parts of the lung are the result of blood - borne (miliary) spread of the organisms.

II **SPLEEN: MILIARY TUBERCULOSIS** **21.95**

Catalogue Number	Small Image	Image Map	Large Image
A_TB_ML_SP_14.jpg	Spleen: Miliary tuberculosis		Spleen: Miliary tuberculosis

Multiple pale nodules throughout the spleen.

III **MILLET SEED - Milium: miliary** **R65.033 & 90.1**

Catalogue Number	Small Image	Image Map	Large Image
A_TB_ML_MS_01.jpg	Millet seed- Millium: miliary		Millet seed- Millium: miliary

IV **LYMPH NODES: TUBERCULOSIS** **28.267**

Extensive destruction and enlargement of lymph nodes by tuberculosis. The friable necrotic ("caseous") material has been partially lost from one of them. From the neck of a 20 year old woman.

V **LUNG & SMALL INTESTINE: POST - PRIMARY TUBERCULOSIS** **P61.667**

Catalogue Number	Small Image	Image Map	Large Image
A_TB_FS_LU_27.jpg	Lung&Small Intestine:Tuberculosis		Lung&Small Intestine:Tuberculosis

Thick, fibrotic pleura with cavitating tuberculosis at the apices and extensive tuberculous bronchopneumonia. **Swallowed** infected sputum has resulted in spread to the Peyer's patches of the ileum.

A 48 year-old man had suffered night sweats and loss of appetite for 4 months with recent weight loss. Extremely ill on admission to hospital, he died 4 days later with massive lung destruction and ulceration of the larynx and small intestine.

VI KIDNEY : TUBERCULOSIS R83.1000A

Catalogue Number	Small Image	Image Map	Large Image
A_TB_TB_KD_07.jpg	Kidney: Tuberculosis		Kidney: Tuberculosis

A kidney with advanced caseous post-primary tuberculosis.

VII SPINE : TUBERCULOSIS 00.164

Catalogue Number	Small Image	Image Map	Large Image
A_TB_TB_SN_01.jpg	Spine: Tuberculosis		Spine: Tuberculosis

Destruction of vertebral bodies with subsequent collapse may result in extreme angulation of the spine (a gibbus). Not only does this cause severe deformity but the spinal cord may be damaged. The arrow indicates the remains of a vertebral body. The other side shows caseation tracking posteriorly to form a 'cold abscess'.

VIII LUNG: PRIMARY COMPLEX WITH MILIARY SPREAD 45.249

From an 8 year old boy who died of miliary tuberculosis and meningitis. There is a peripheral yellow nodule (**GHON FOCUS** - the site of primary infection) in the inferior part of the lower lobe and enlarged hilar lymph nodes, which together constitute the **PRIMARY COMPLEX**. Scattered miliary lesions are present, most numerous beneath the pleura.

Catalogue Number	Small Image	Image Map	Large Image
A_TB_ML_LU_11.jpg	Lung: Primary complex with miliary spread		Lung: Primary complex with miliary spread

IX LUNG: MILIARY TUBERCULOSIS 41.65

Catalogue Number	Small Image	Image Map	Large Image
A_TB_ML_LU_12.jpg	Lung: Miliary tuberculosis		Lung: Miliary tuberculosis

Discrete tuberculous granulomas are scattered throughout this lung.

An 18 year old girl, ill for two weeks with cough and headache gradually became comatose and died. She had meningitis, miliary tuberculosis and a caseating lesion in the other lung, which was the source of her widespread disease.

**X LYMPH NODES: TUBERCULOSIS
S56.3743**

Catalogue Number	Small Image	Image Map	Large Image
A_TB_FS_LN_01.jpg	Lymph nodes: Tuberculosis	Image map	Lymph nodes: Tuberculosis

Enlarged nodes, present about nine months in the neck of an 18 year old girl, contain irregular areas of tuberculous ("caseous") necrosis. No other evidence of infection was found. Where might the primary site have been ?

**XI LUNG: POST-PRIMARY TUBERCULOSIS
R64.310**

Catalogue Number	Small Image	Image Map	Large Image
A_TB_FS_LU_26.jpg	Lung: Post-primary tuberculosis		Lung: Post-primary tuberculosis

From a 53 year old man with cough and weight loss. There is cavitating apical tuberculosis of both lungs and tuberculous bronchopneumonia. The pleura shows fibrotic thickening.

**XII KIDNEY : TUBERCULOSIS
P64.706**

Catalogue Number	Small Image	Image Map	Large Image
A_TB_TB_KD_05.jpg	Kidney: Tuberculosis		Kidney: Tuberculosis

A kidney almost destroyed by advanced caseous post primary tuberculosis.

**XIII SPINE : TUBERCULOSIS
45.293**

Catalogue Number	Small Image	Image Map	Large Image
A_TB_TB_SN_02.jpg	Spine: Tuberculosis		Spine: Tuberculosis

There is destruction of an intervertebral disc and bilateral extension into the psoas sheath. Downward spread within the latter may result in a 'cold abscess' in the inguinal region.