Diagnosis and Treatment of Non Hodgkin's Lymphomas (NHL)

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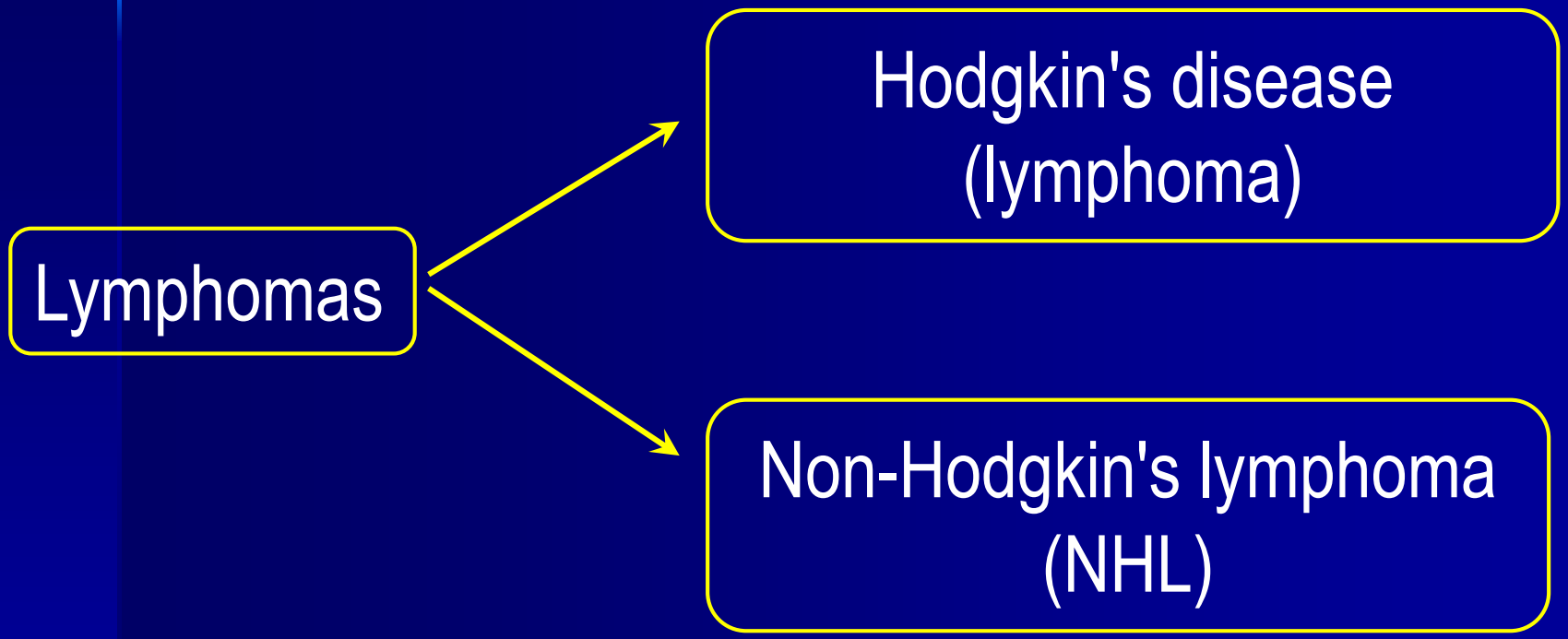
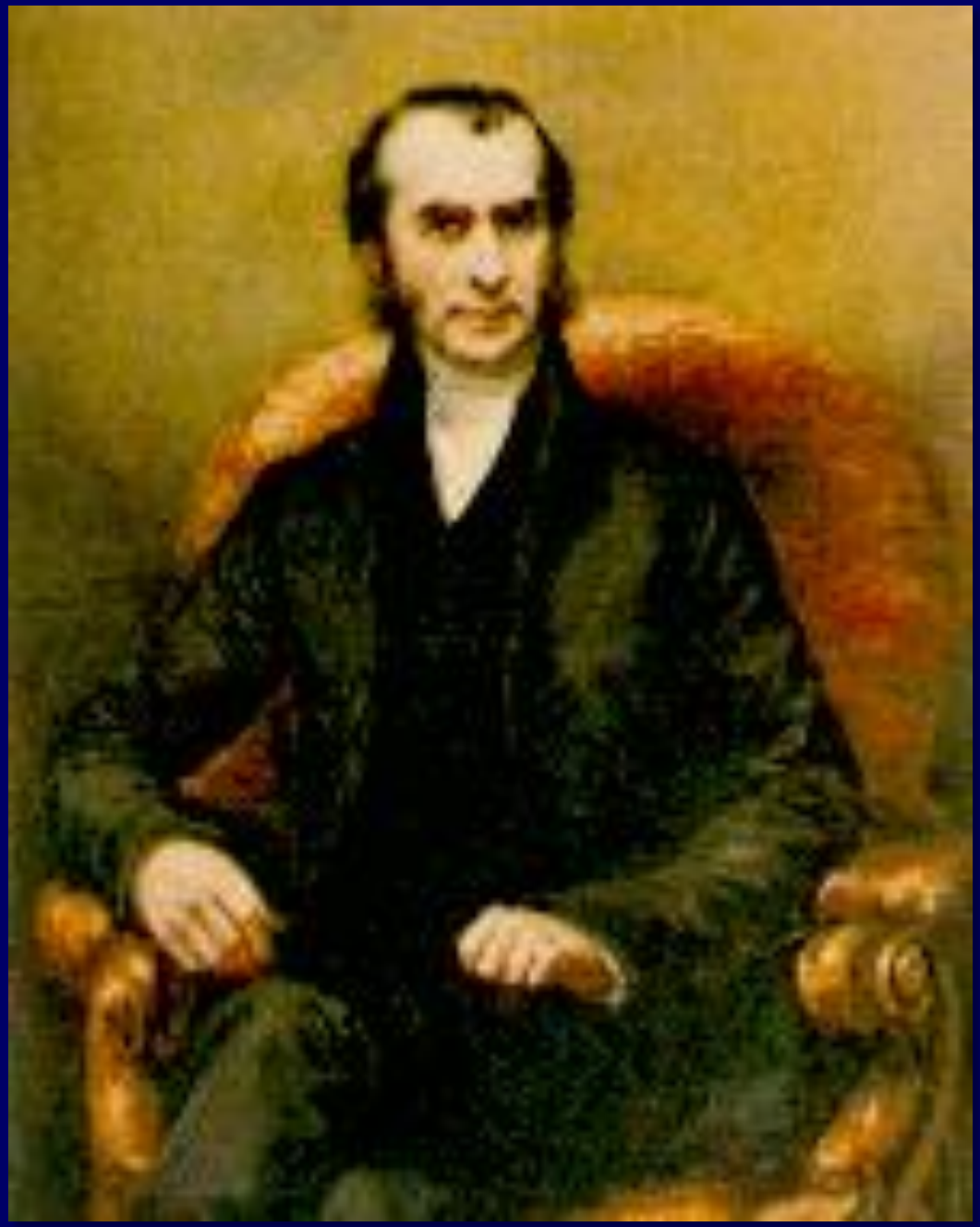
Lymphoma group





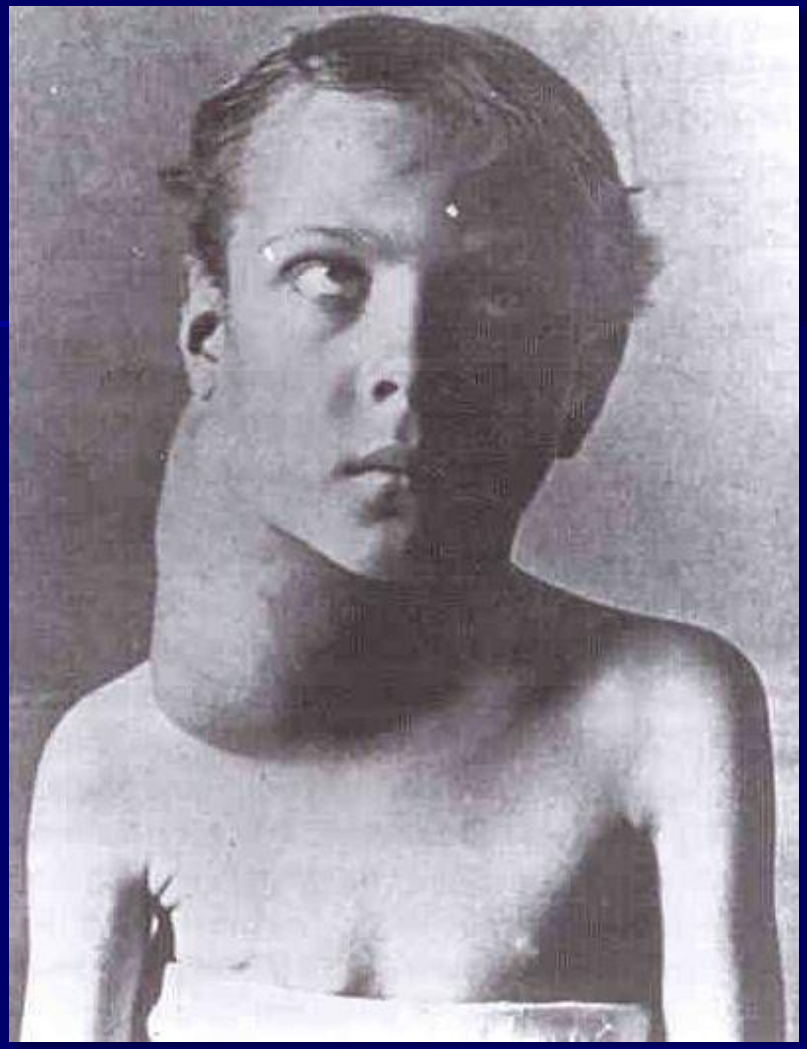
Thomas Hodgkin
(1798 – 1866)

Hodgkin's disease

- Thomas Hodgkin (1798 – 1866)
- In 1832 T.Hodgkin published an article "On some morbid appearances of absorbent glands and spleen" in the magazine "Medico-Chirurgical Transactions”
  - On 6 August 1828, 10 year old boy Ellenborough King arrives at the hospital with a distinctly swollen lymph nodes and spleen
  - On 23 September 1828, the patient dies. Autopsy is conducted. This case was histologically confirmed also in the 20th century.

Hodgkin's and Non-Hodgkin's lymphomas

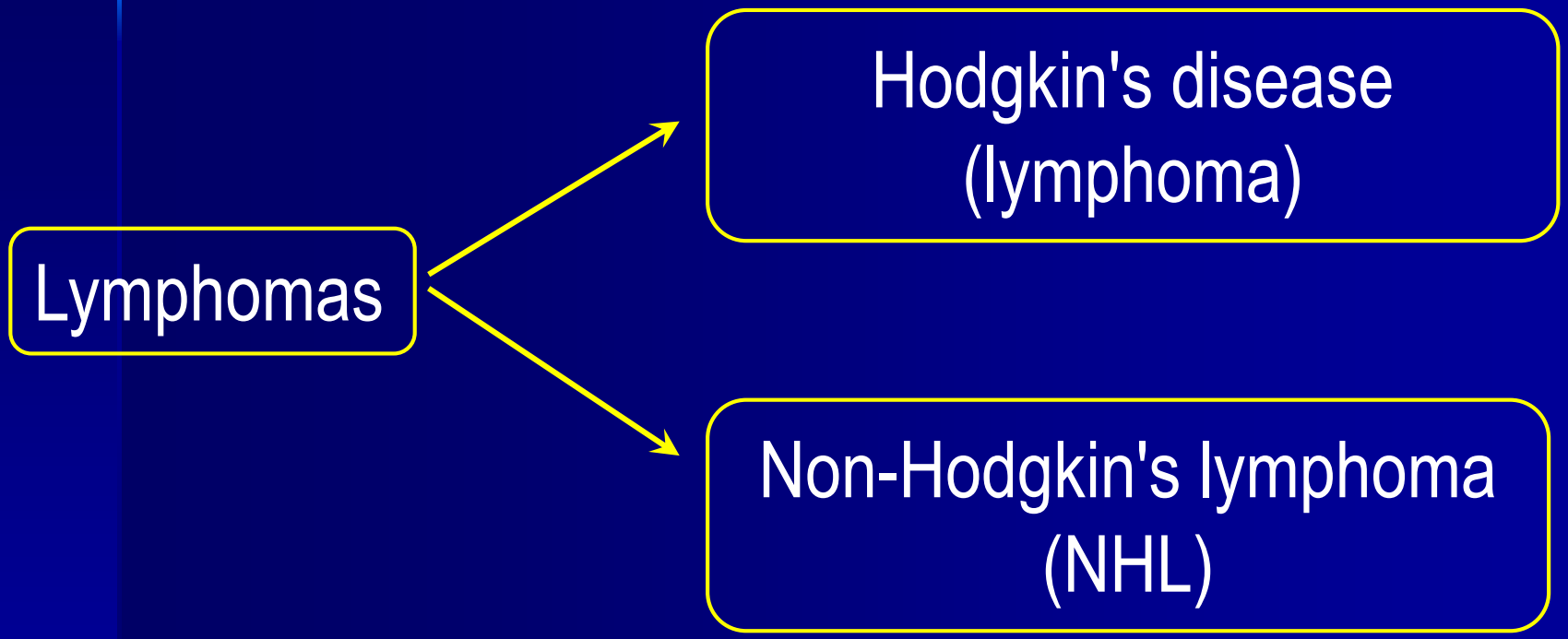
- In 1856 and 1865 Sir Samuel Wilks described similar cases. He was the first to use the term "Hodgkin's disease"
- Later similar diseases are described, but they are already named Non-Hodgkin's lymphoma
- 1902 – the first instance of treating Hodgkin's disease with radiation
- 1946 – chemotherapy is used for the first time (nitrogen mustard)



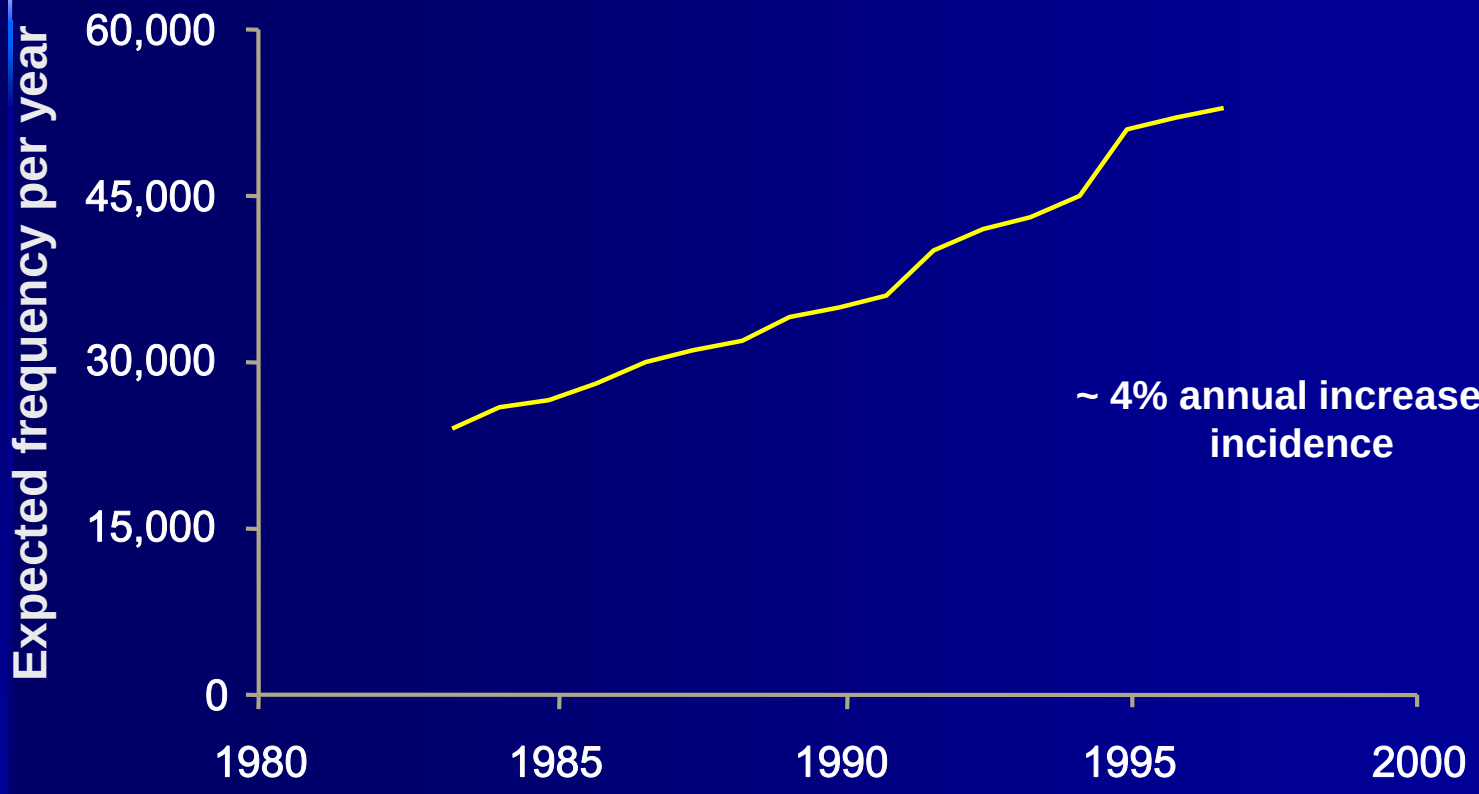
A 7 – year – old boy (W.D.M., Case 7)
in Dorothy Reed's classic paper,
showing similar presentation to Ellenborough King. (1902)

2000 Blackvell Science Ltd. British Journal of Haematology 109

Lymphoma group

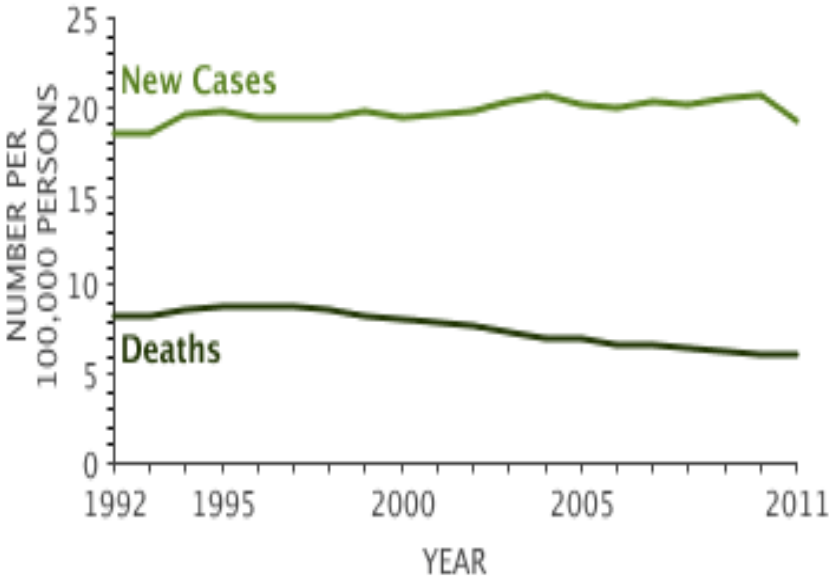


Over the past 20 years NHL increases by 3 - 4% per year



Adapted from Greenlee et al. *CA Cancer J Clin.* 2001;51:15.

Estimated New Cases in 2014	70,800
% of All New Cancer Cases	4.3%
Estimated Deaths in 2014	18,990
% of All Cancer Deaths	3.2%



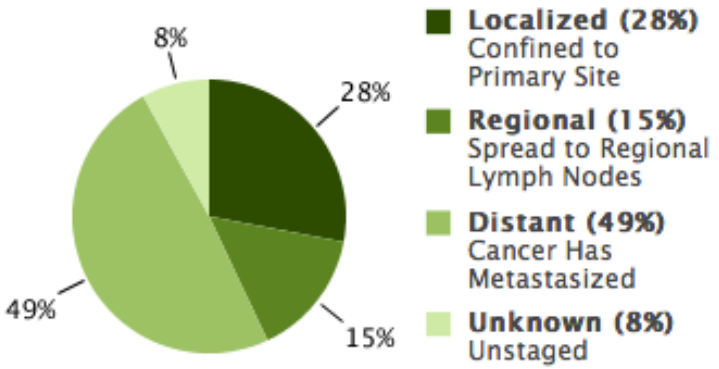
Percent Surviving 5 Years

69.3%

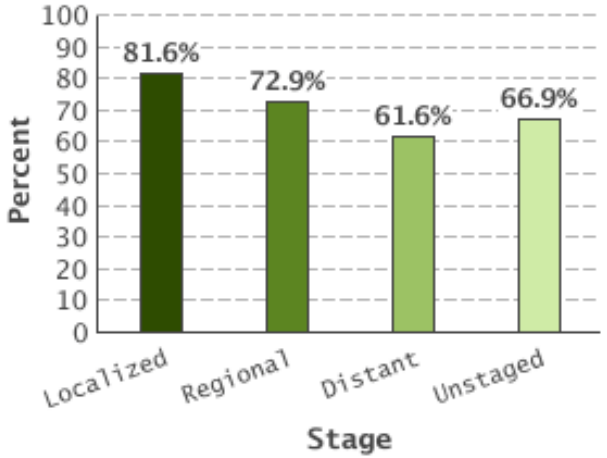
2004–2010

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Non-Hodgkin Lymphoma

Percent of Cases by Stage



5-Year Relative Survival



SEER 18 2004-2010, All Races, Both Sexes by SEER Summary Stage 2000

Increase in the incidence of NHL

- From 1975 to 2005 NHL increase was +80%
- NHL – 53% of all haematological malignancies
- The number of immunosuppressive patients increases – number of NHL patients increases
  - HIV/AIDS
  - patients after organ transplantation
  - 27% of NHL patients in the USA have immunosuppression

Number of New Cases and Deaths per 100,000

- The number of new cases of non-Hodgkin lymphoma was 19.7 per 100,000 men and women per year
- The number of deaths was 6.3 per 100,000 men and women per year
- These rates are age-adjusted and based on 2007-2011 cases and deaths

National Cancer Institute (US)

Lifetime Risk of Developing NHL

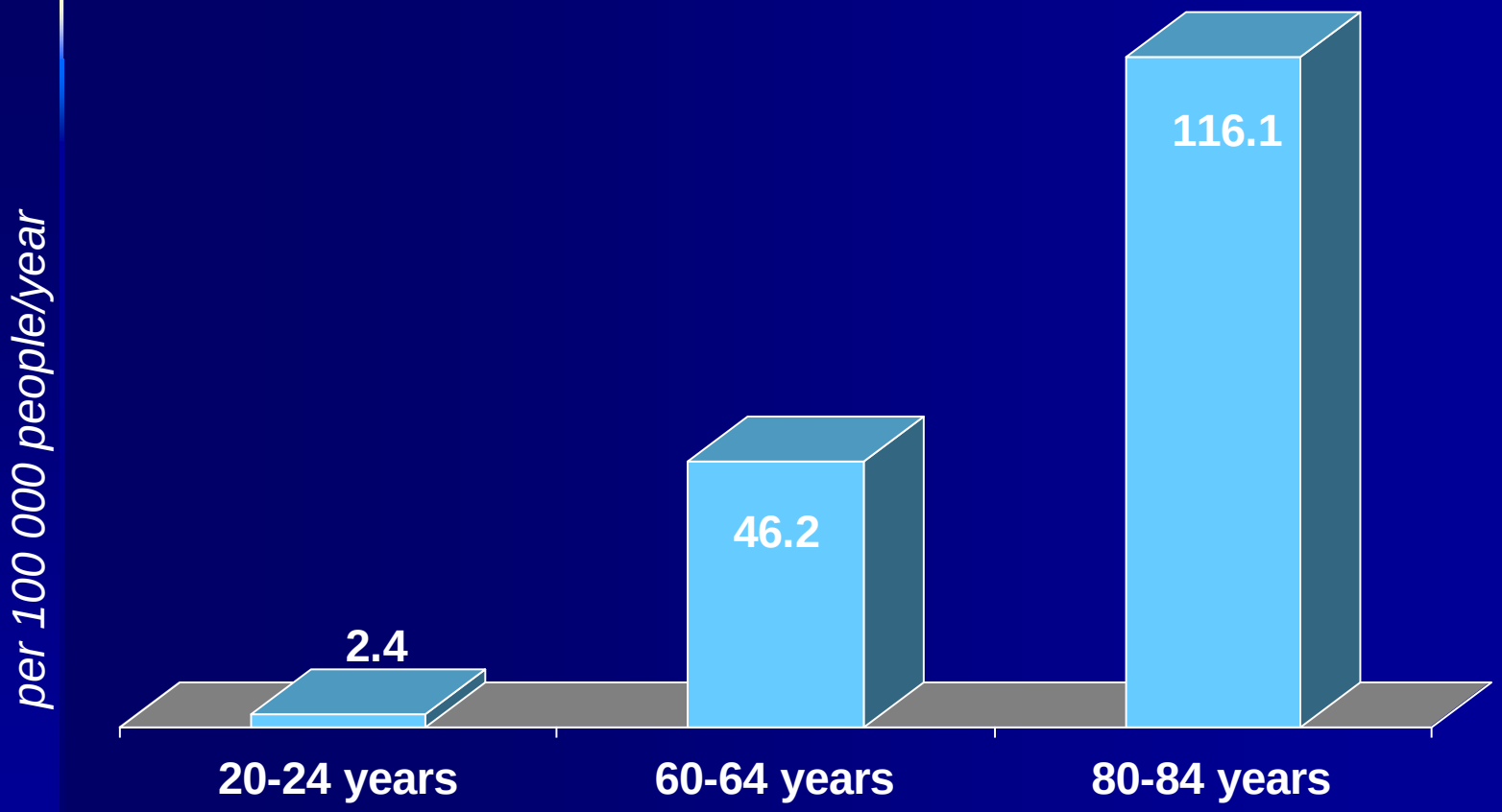
- Approximately 2.1 per cent of men and women will be diagnosed with non-Hodgkin lymphoma at some point during their lifetime, based on 2009-2011 data
- In 2011, there were an estimated 530,919 people living with non-Hodgkin lymphoma in the United States

National Cancer Institute (US)

HIV - associated lymphomas

- In 1981 – the first patient with HIV was described
- In 1982 – the first HIV associated lymphoma case
- After Kaposi's sarcoma the second most common tumour in HIV patients
- Most common extramedullary localization
  - CNS
  - Digestive tract
  - Bone marrow
  - Liver

NHL in different age groups



Non-Hodgkin's lymphomas

DEFINITION

- Non-Hodgkin's lymphoma (NHL) is a malignant tumour in lymphoid tissue in lymph nodes or other sites of lymphoid tissue localisation
  - may be of B or T lymphocyte origin

  In cases of NHL the growth, proliferation and metastazing of malignant lymphoid cells takes place.

NHL – a group of heterogeneous diseases

- Both B and T cell lymphomas.
- Lymphomas of both low and high malignancy, with different clinical presentation, treatment and prognosis.
- It must be kept in mind that the concepts of low and high malignancy in cases of NHL differ from cases of solitary tumours
  - Low grade NHL process progresses comparatively slower
  - In cases of high grade NHL the lymphoid cells are younger, they divide and proliferate faster, the malignant process tends to progress faster.

ETIOLOGY

- NHL etiology is not completely clear
- Important risk factors are:
  - radiation,
  - toxic chemicals,
  - virus infections.
- Immunosuppressive conditions are significant in NHL origination
- Hereditary immunosuppressive conditions as a syndrome are linked with more frequent development of lymphomas:
  - Wiskott-Aldrich syndrome
  - Syndrome of ataxia-telangiectasia

ETIOLOGY

- Patients with HIV infection related immunosuppression or following the use of immunosuppressive drugs after organ transplantation develop NHL more frequently than the rest of the population of the respective age
- Among HIV patients, as to to the frequency of secondary tumours, lymphomas rate as second after Kaposi's sarcoma
  - Primary CNS lymphomas
  - Liver lymphomas
- In recent years a trend is observed that increasingly younger patients develop the disease

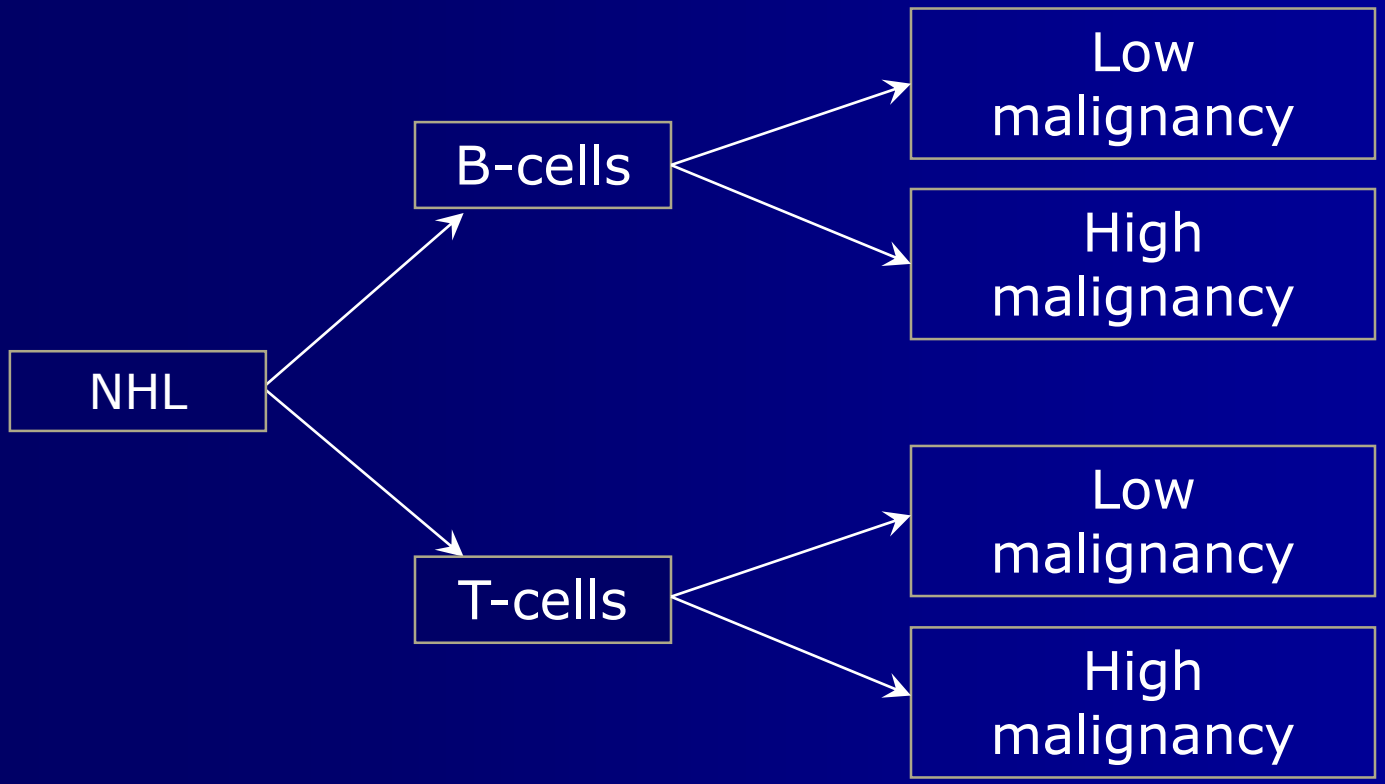
ETIOLOGY

- The following chemical factors are regarded as possible risk factors:
  - vinyl chloride,
  - rubber,
  - pesticides, insecticides,
  - chemical solvents,
  - risk related vocations are rubber and leather production, dyeing, agriculture

ETIOLOGY

- The following have also been noted as possible pathogenic factors:
  - Epstein-Barra virus in the case of Burkitt's lymphoma
  - HTLV-I acute T-cell lymphoma/leukaemia

NHL classification



CLINICAL PRESENTATION

- Clinical presentation significantly differs in low and high malignancy lymphomas
- At the very onset of the disease there may be cases, when the patient himself detects enlarged lymph nodes, the lymph nodes are usually not painful to touch, therefore quite often the patient does not go to see a doctor
- In cases of low malignancy NHL lymphomas, the enlargement of lymph nodes can already be pronounced, but the patient has no complaints

CLINICAL PRESENTATION

- In all cases where a patient has enlarged lymph nodes and the cause is unclear, NHL is one of the possibilities, the diagnosis needs histological confirmation

Clinical presentation

- In NHL cases patients may also complain of:
  - tiredness,
  - feebleness,
  - decreased capacity for work,
  - poor appetite, weight loss,
  - increased perspiration,
  - subfebrile temperature
- In cases of high malignancy NHL temperature can be pronounced, a typical picture of intoxication may develop
- In some cases of high malignancy NHL, for example, in cases of angioimmunoblastic lymphadenopathy febrile temperature, perspiration, weight loss develop, lymph nodes become enlarged, hepatosplenomegaly is found, changes in skin with pronounced itching

Clinical presentation

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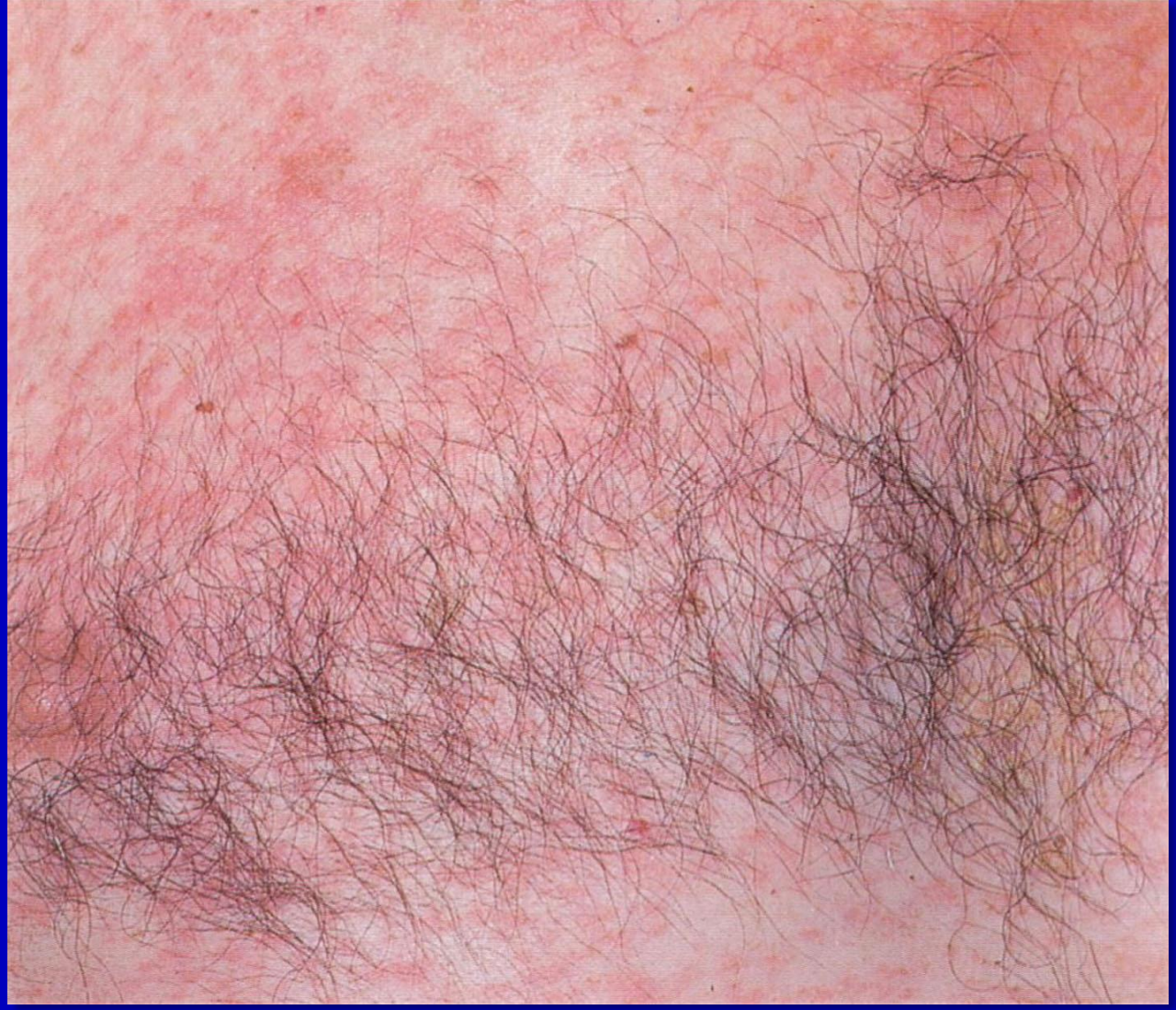
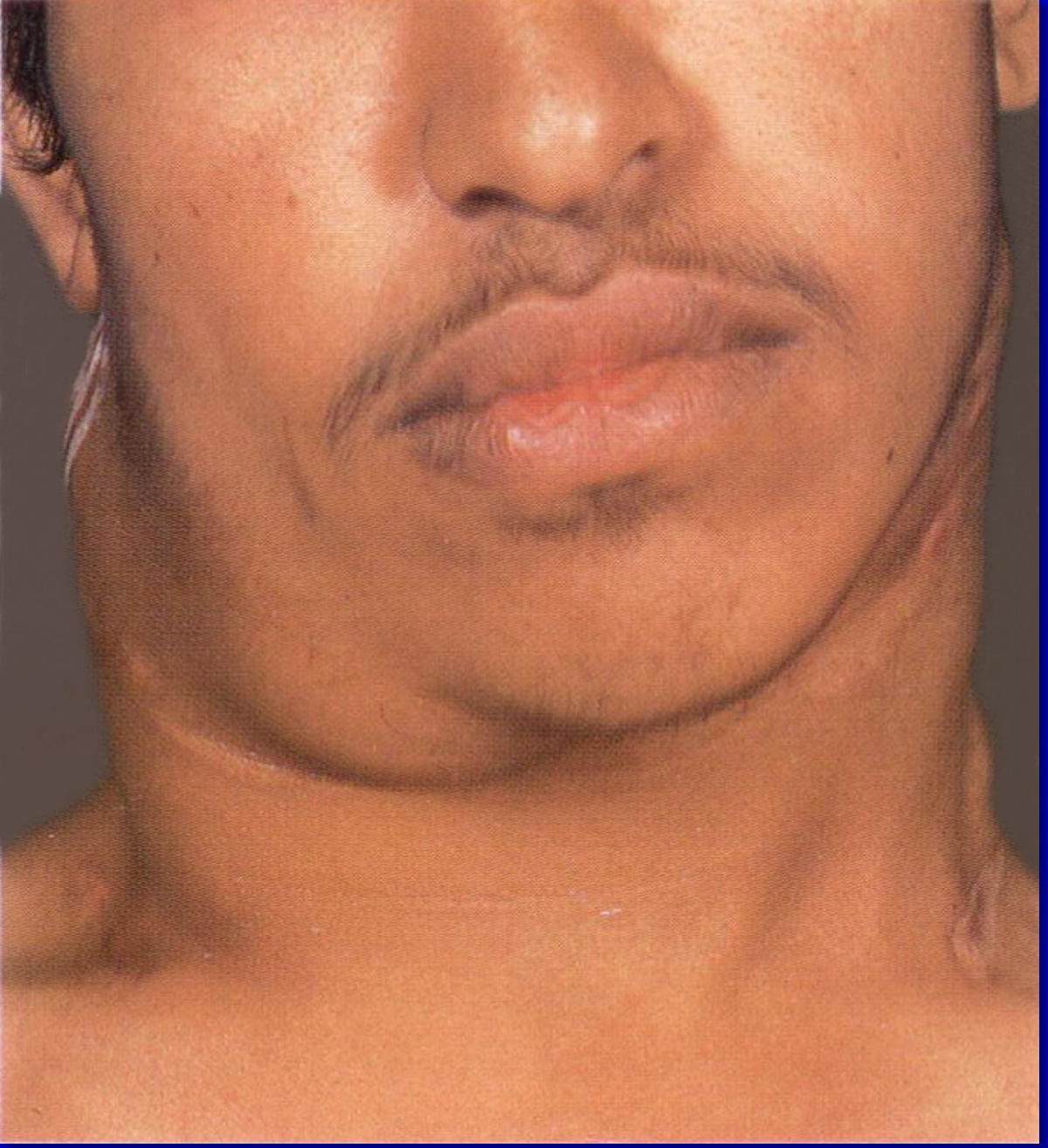


NHL. Angioimmunoblastic lymphadenopathy.
Skin erythematous, clinically - marked skin itching

«Clinical Haematology» 1994/A. Victor Hoffbrand, John E. Pettit

Clinical presentation

- The most typical clinical feature are enlarged lymph nodes, they are usually enlarged asymmetrically (in difference to chronic lymphocytic leukemia), not painful upon palpation
- In cases of low malignancy NHL, there is no intergrowth of lymph nodes, nor with surrounding tissue
- In cases of high malignancy NHL lymph nodes feel denser when palpated, they tend to form a conglomerate, they may have intergrown and may have infiltrated into skin, surrounding muscles



Explicit neck lymphadenopathy

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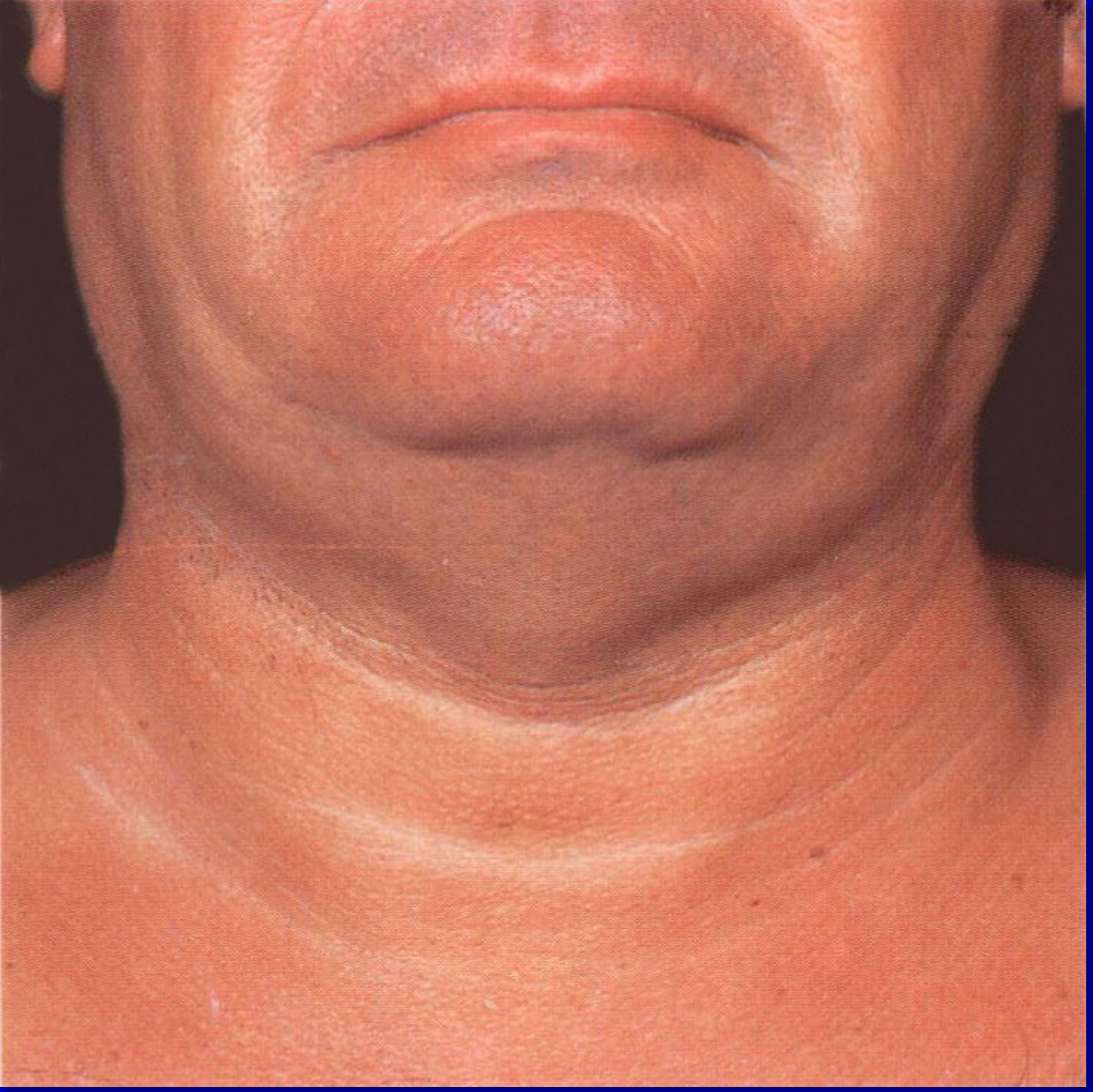
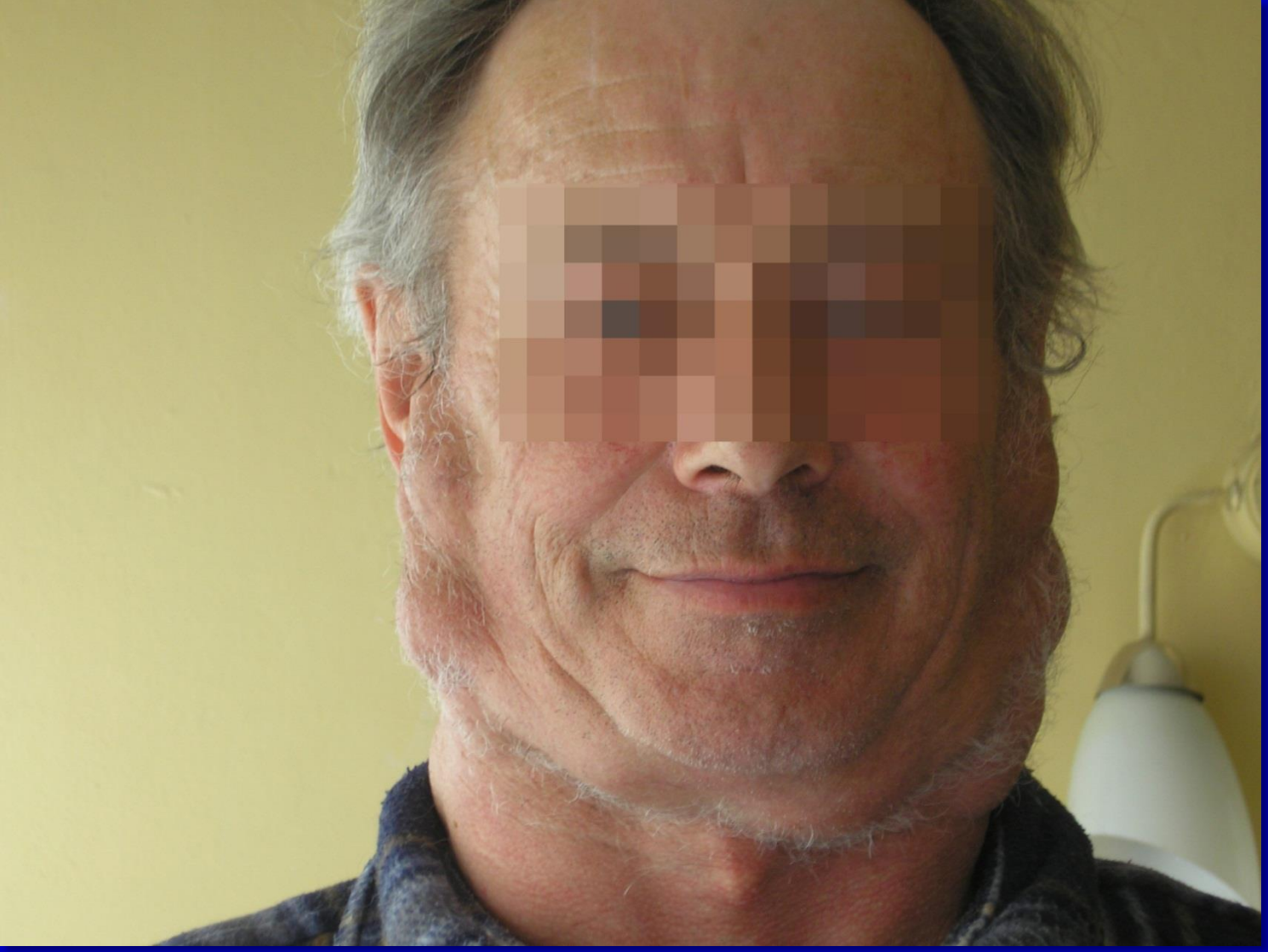
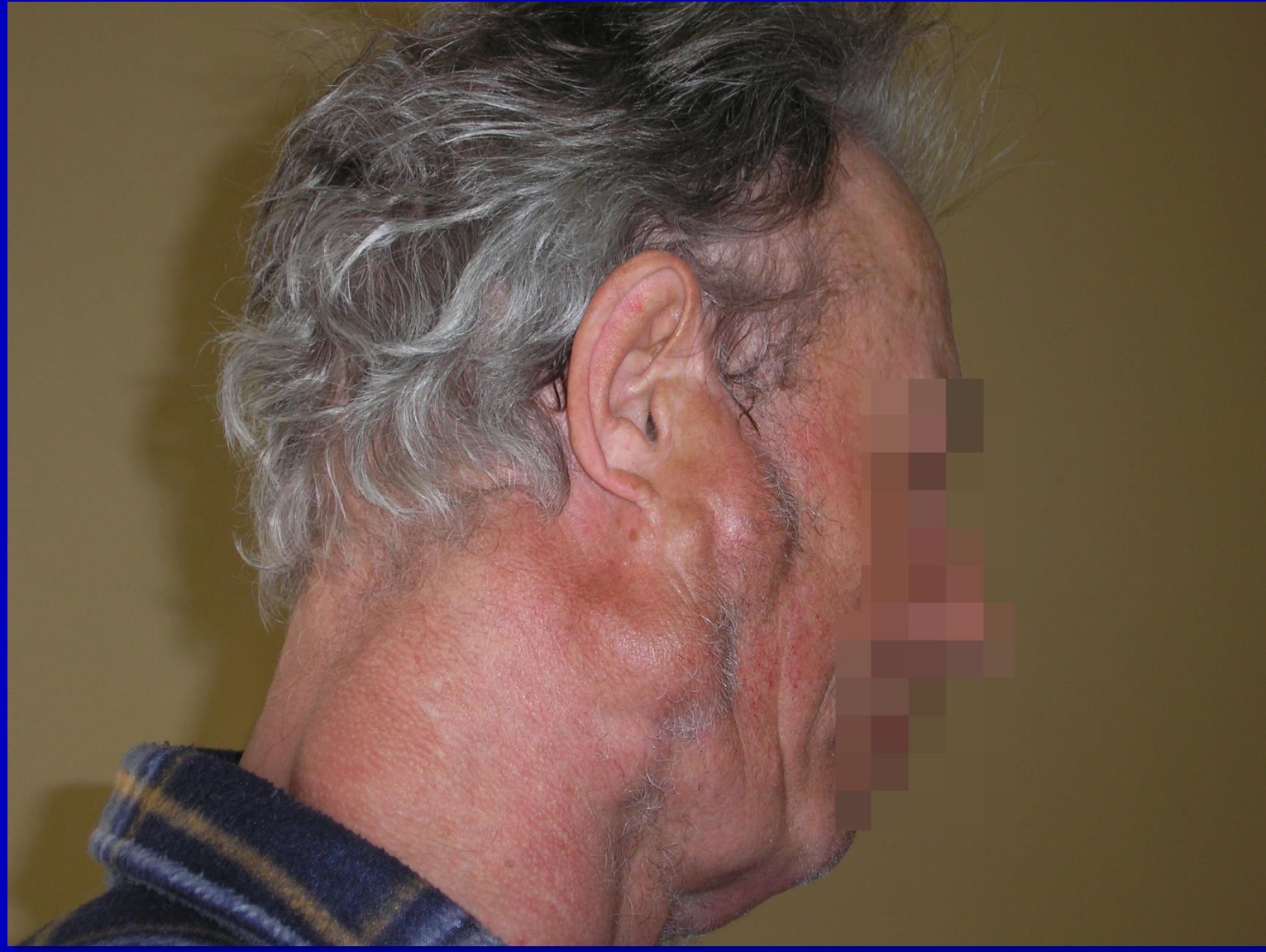


Non-Hodgkin's lymphoma. Increase of the cervical lymph nodes.

«Clinical Haematology» 1994/A. Victor Hoffbrand, John E. Pettit



Non-Hodgkin's lymphoma, follicular, stage IV

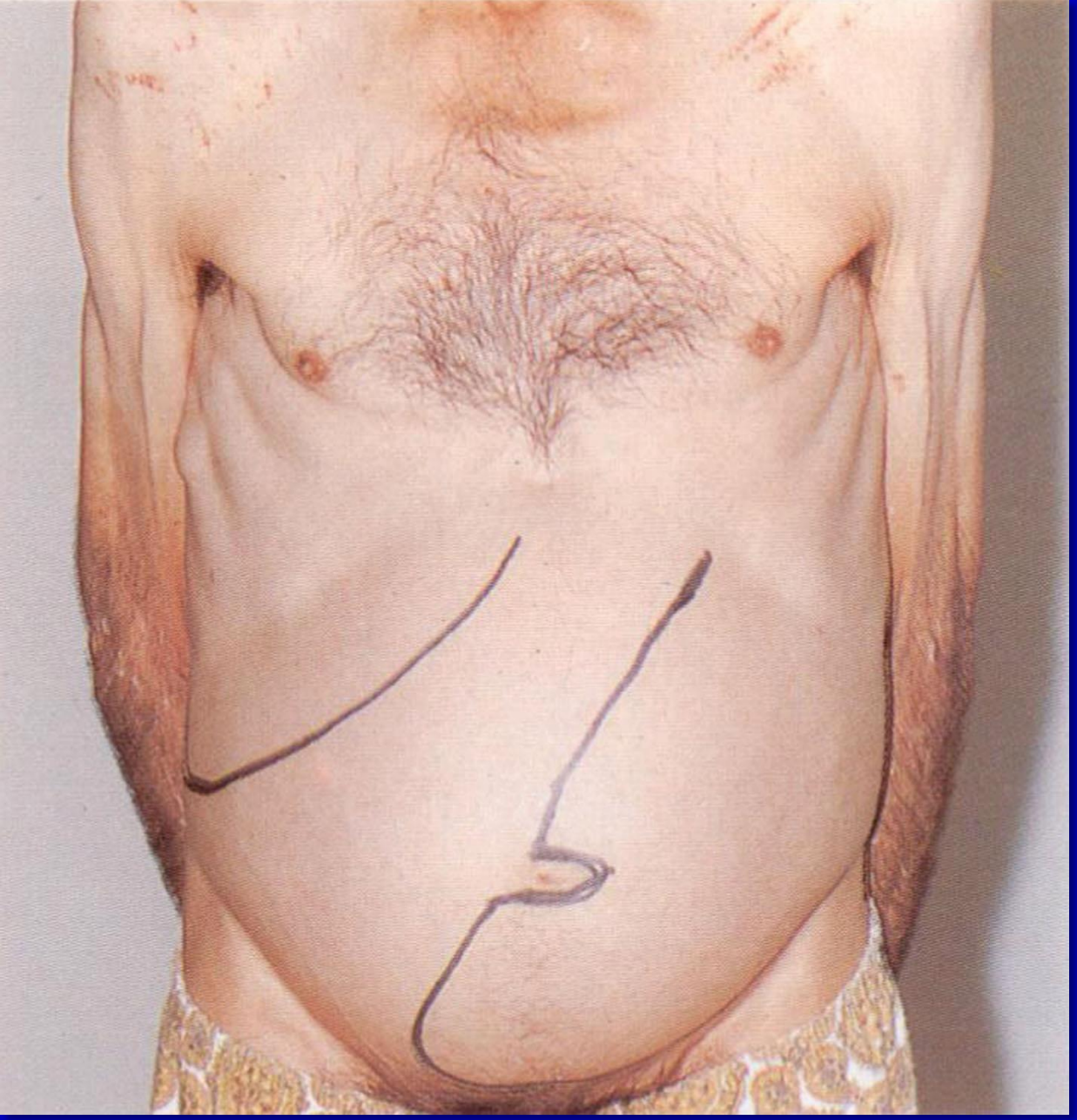


Non-Hodgkin's lymphoma, follicular, stage IV

Non-Hodgkin's lymphoma, follicular, stage IV

CLINICAL PRESENTATION

- In NHL, in difference to Hodgkin's disease, the typical localisation is outside lymph nodes.
- Quite frequently already at the moment of diagnosis splenomegaly is also found, as well as enlarged liver, changes in lungs, tonsils, stomach, intestines, skin, bone marrow.
- In NHL cases the primary localisation may be outside lymph nodes, in such cases often other tumours are considered, however, the diagnosis of a lymphoma is confirmed morphologically.
- Outside lymph nodes primary NHL may be also in the spleen, liver, stomach, CNS, tonsils, thyroid, intestines, skin, bone marrow, lungs, pleura, kidneys.



Non-Hodgkin's lymphoma
Hepatomegaly
Splenomegaly

«Clinical Haematology» 1994/A. Victor Hoffbrand, John E. Pettit

LABORATORIAL CHANGES

- In the initial stage of NHL it is possible that no changes in peripheral blood or biochemical indicators are found.
- Later changes are found, and they are the following:
  - Elevated ESR
  - Leucocytosis with absolute lymphocytosis
    - These changes may remind of the blood count in cases of chronic lympholeukemia
    - In cases of NHL part of lymphocytes have been morphologically changed

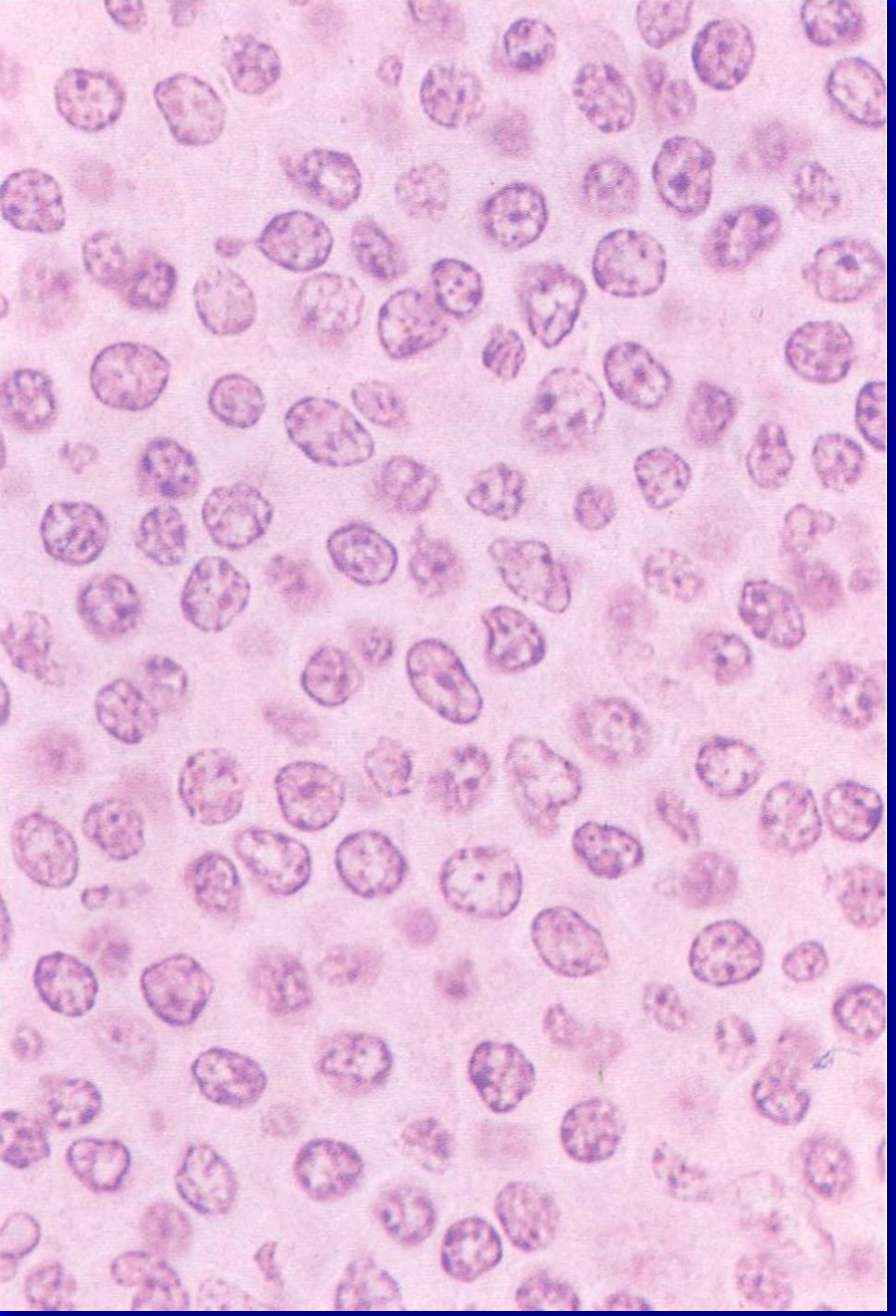
LABORATORICAL CHANGES

- Anaemia may have a number of causes:
  - Lymphoid infiltration of bone marrow;
  - The number of red line cells in bone marrow decreases;
  - Autoimmune haemolytic.
- Thrombocytopenia develops:
  - secondarily, due to lymphoid infiltration of bone marrow;
  - due to autoimmune bodies.

Laboratorial changes

- Leukopenia with neutropenia of various degrees
- Pancytopenia in blood at the moment of diagnosing the disease in patients with bone marrow infiltration or pronounced splenomegaly
- Elevated CRP
- Elevated LDH level
  - poor prognostic criterion
- Decreased albumin
  - poor prognostic sign
- Elevated beta-2-microglobuline
  - poor prognostic sign
- Elevated IL-6 level
- Paraprotein may be found in blood

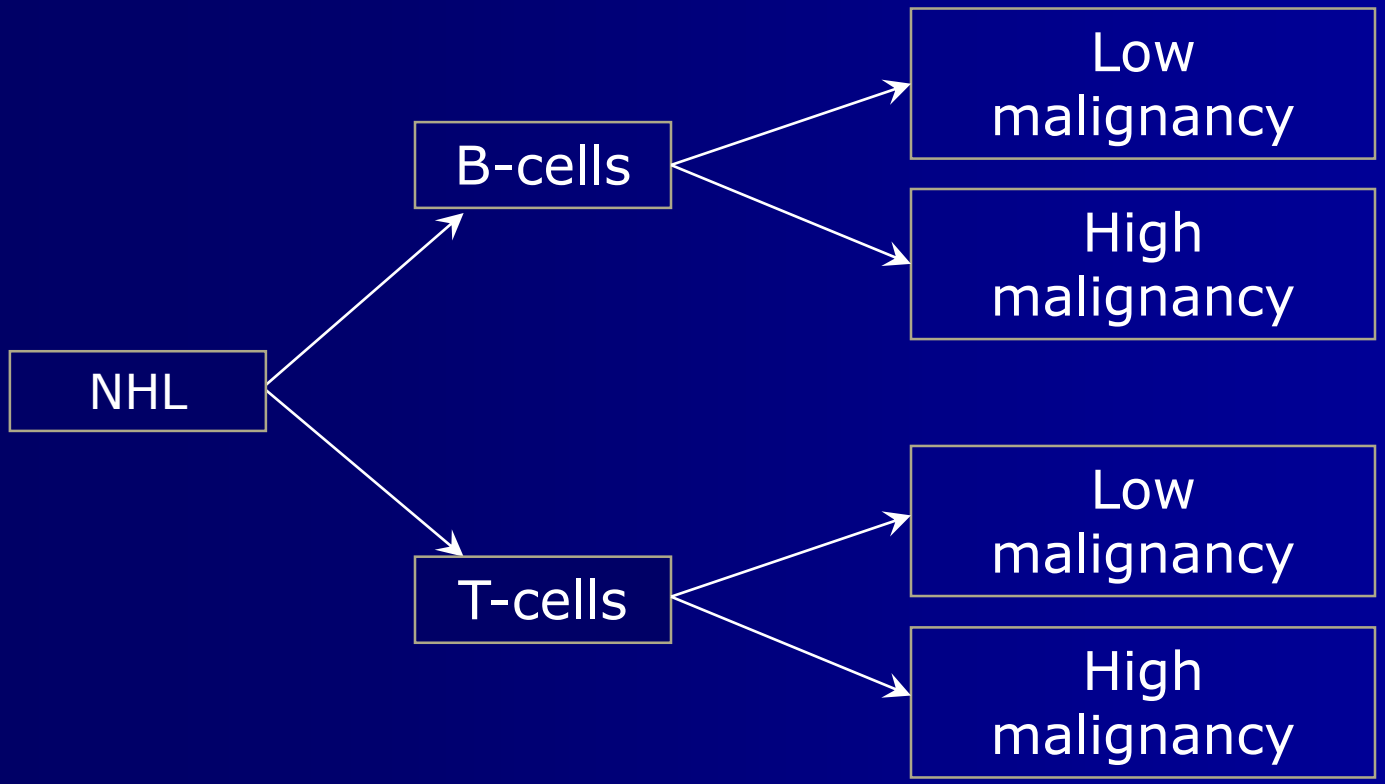
The main diagnostic criterion of Non-Hodgkin's lymphomas is the histological conclusion regarding the biopsy material

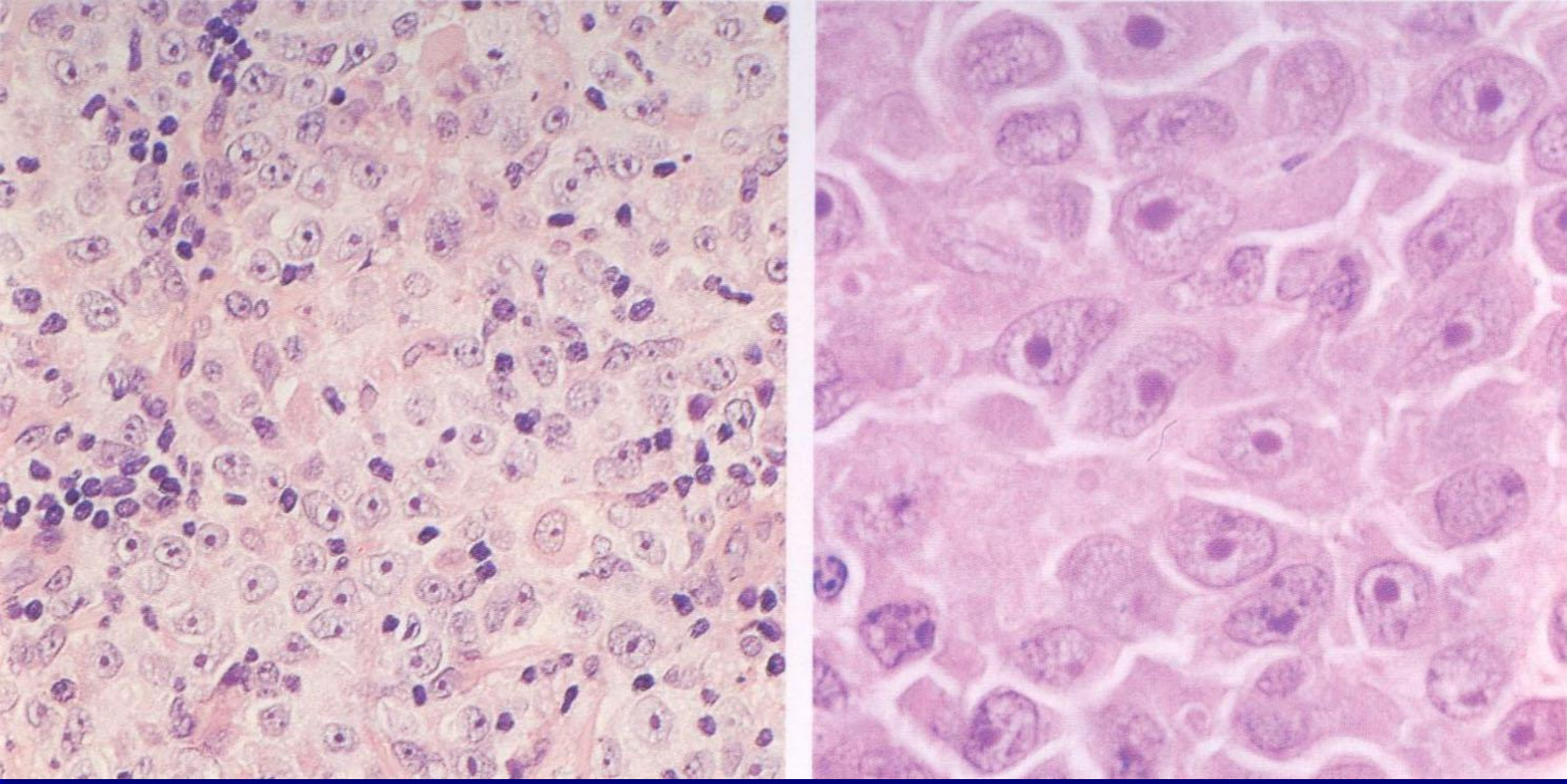


**Non-Hodgkin's lymphoma.
Histological preparation.
Lymphocyte infiltration.**

«Clinical Haematology» 1994/A. Victor Hoffbrand, John E. Pettit

NHL classification



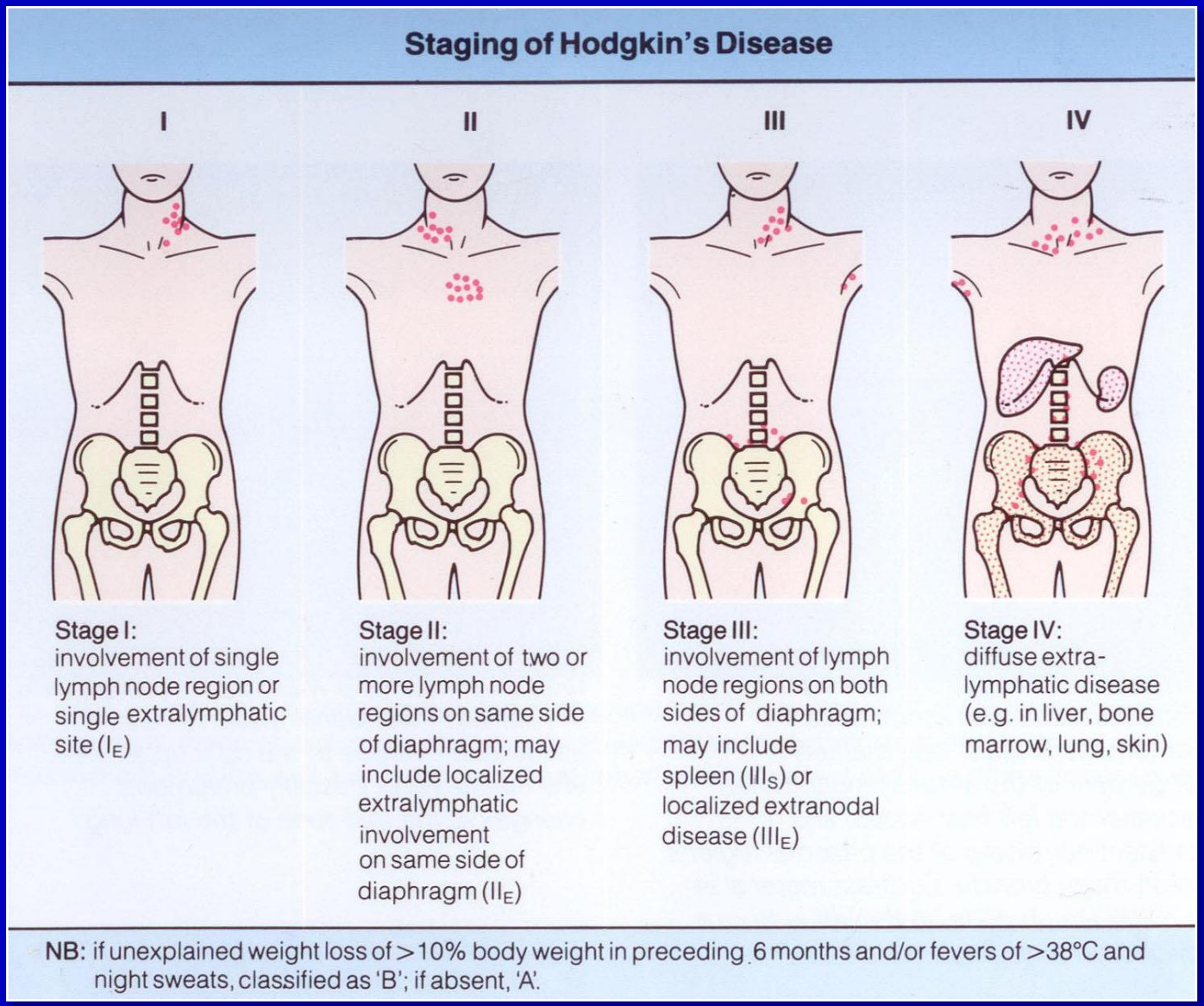


Non-Hodgkin's lymphoma. Histological preparations. Immunoblastic lymphoma

«Clinical Haematology» 1994/A. Victor Hoffbrand, John E. Pettit

NHL diagnostics

- Biopsy and histological conclusion
  - Immunohistochemistry
- Stage of NHL
  - CT, MRI
  - PET Scan



Hodgkin's disease and NHL Stage classification.

«Clinical Haematology» 1994/A. Victor Hoffbrand, John E. Pettit

CT limits

- Can not determine that lymph nodes are involved in the process, which are a normal size
- Relatively poor sensitivity to detect extranodal damages

The more accurately lymphoma spread is evaluated - the more accurate and better is the treatment

PET

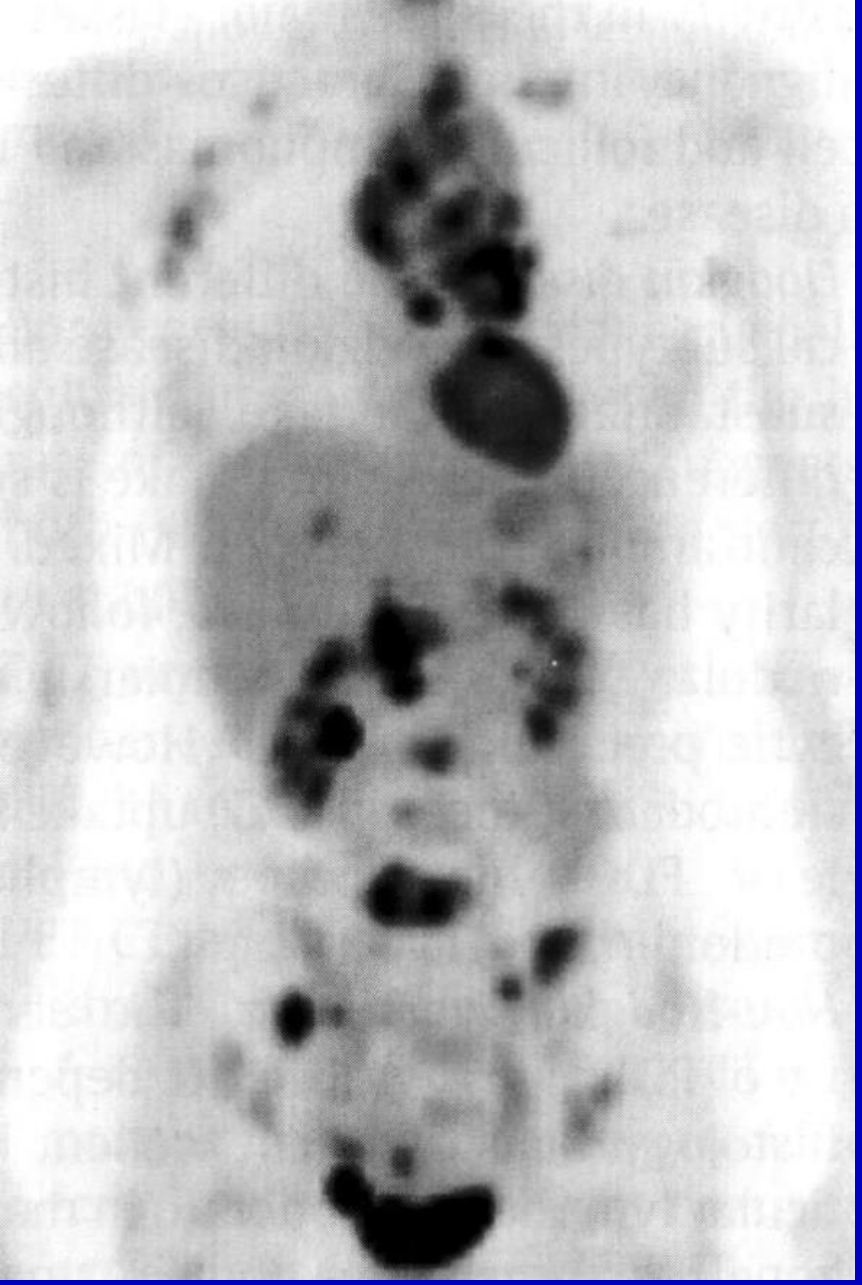
- PET –[(18)] fluoro-deoxy-d-glucose positron emission tomography (FDG-PET)
- Determines increased glycolysis, that is a typical characteristic of tumour metabolism

PET advantages

- Is able to determine cell activity in cases where it can't be diagnosed by CT
  - Active disease
  - Relapse
  - Therapy effectiveness assessment

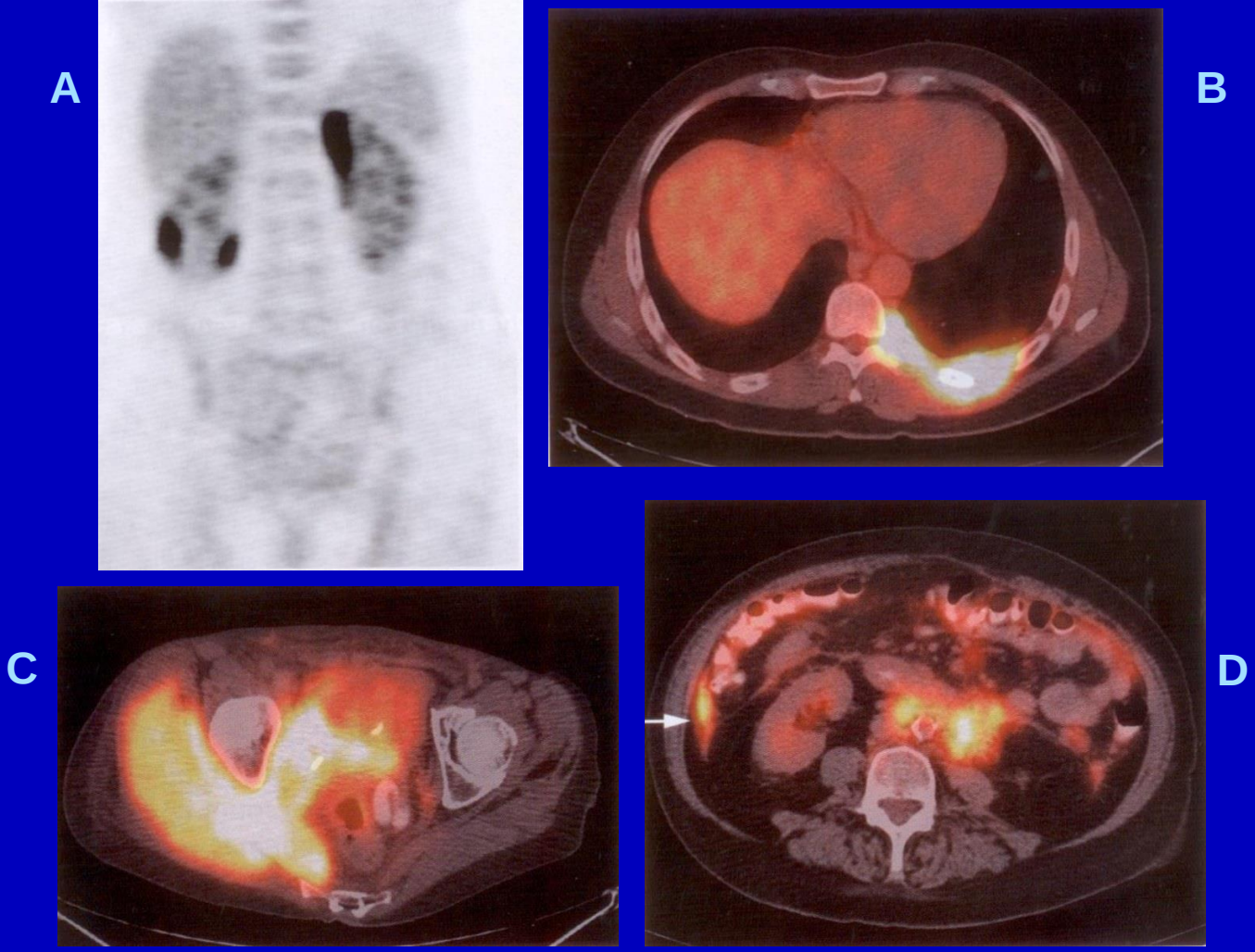
PET use

- Stage determination for first-time patients
- Evaluation of treatment results after chemotherapy
- After a few courses of chemotherapy
- Relapse, especially atypical localizations
- Before high dose chemotherapy and transplantation of autologous stem cells



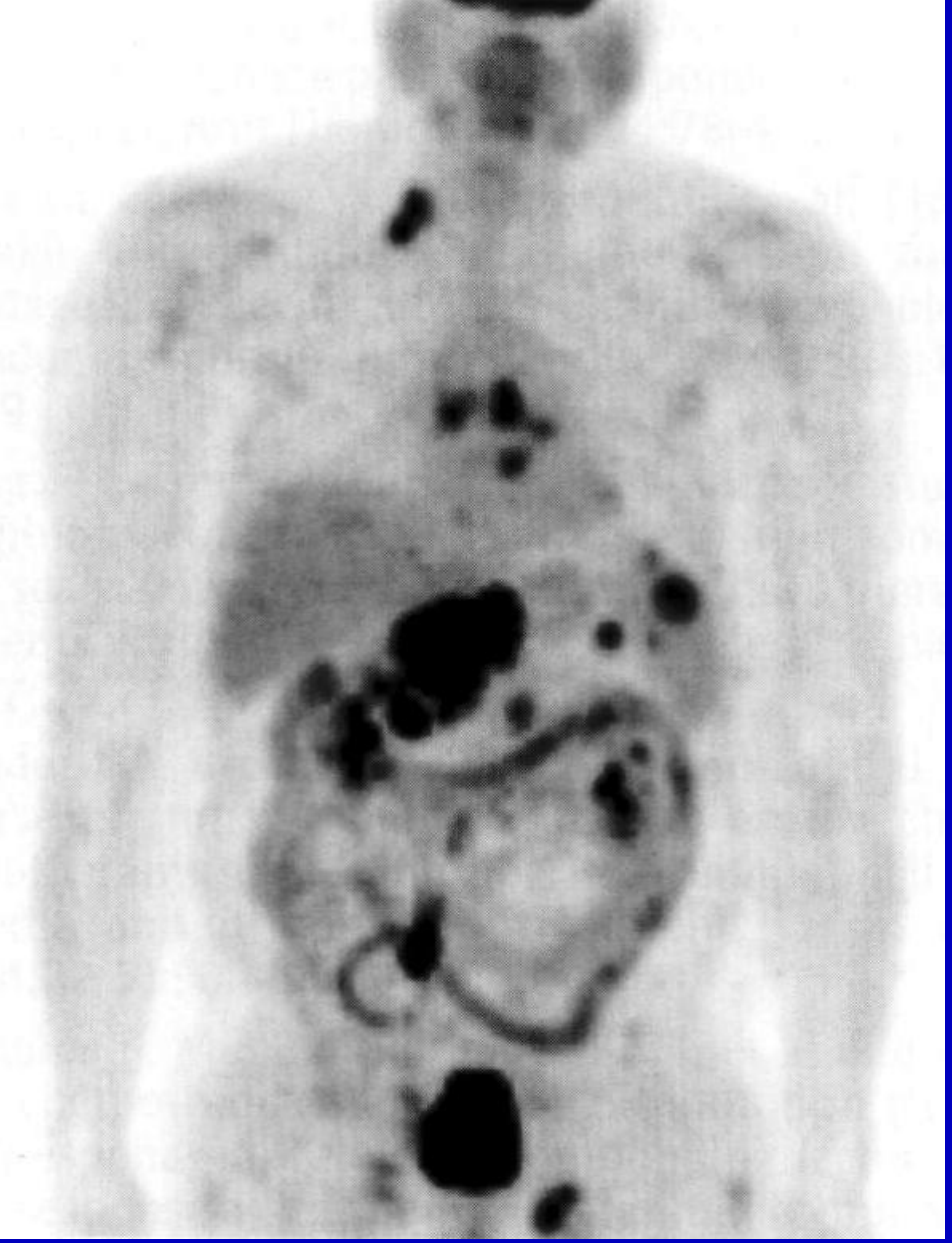
Extensive lymphoma. Coronal positron emission tomography scan in a patient with non-Hodgkin lymphoma demonstrates uptake in mediastinal, supraclavicular, axillary, and retroperitoneal nodes, liver, and bone marrow (pelvis and lumbar spine).

«PET and PET/CT: A clinical Guide» Second Edition 2005/ Eugene C. Lin, Abass Alavi



Lymphoma: spectrum of disease. Positron emission tomography (PET) and PET/computed tomography scans in different patients with non-Hodgkin lymphoma demonstrate disease involving the (A) perirenal space, (B) pleura, (C) muscle, and (D) peritoneum (*arrow*).

«PET and PET/CT: A clinical Guide» Second Edition 2005/ Eugene C. Lin, Abass Alavi



Extensive lymphoma. Coronal positron emission tomography scan in a patient with non-Hodgkin lymphoma demonstrates uptake in mediastinal, supraclavicular, abdominal, pelvic, and groin nodes and the spleen.

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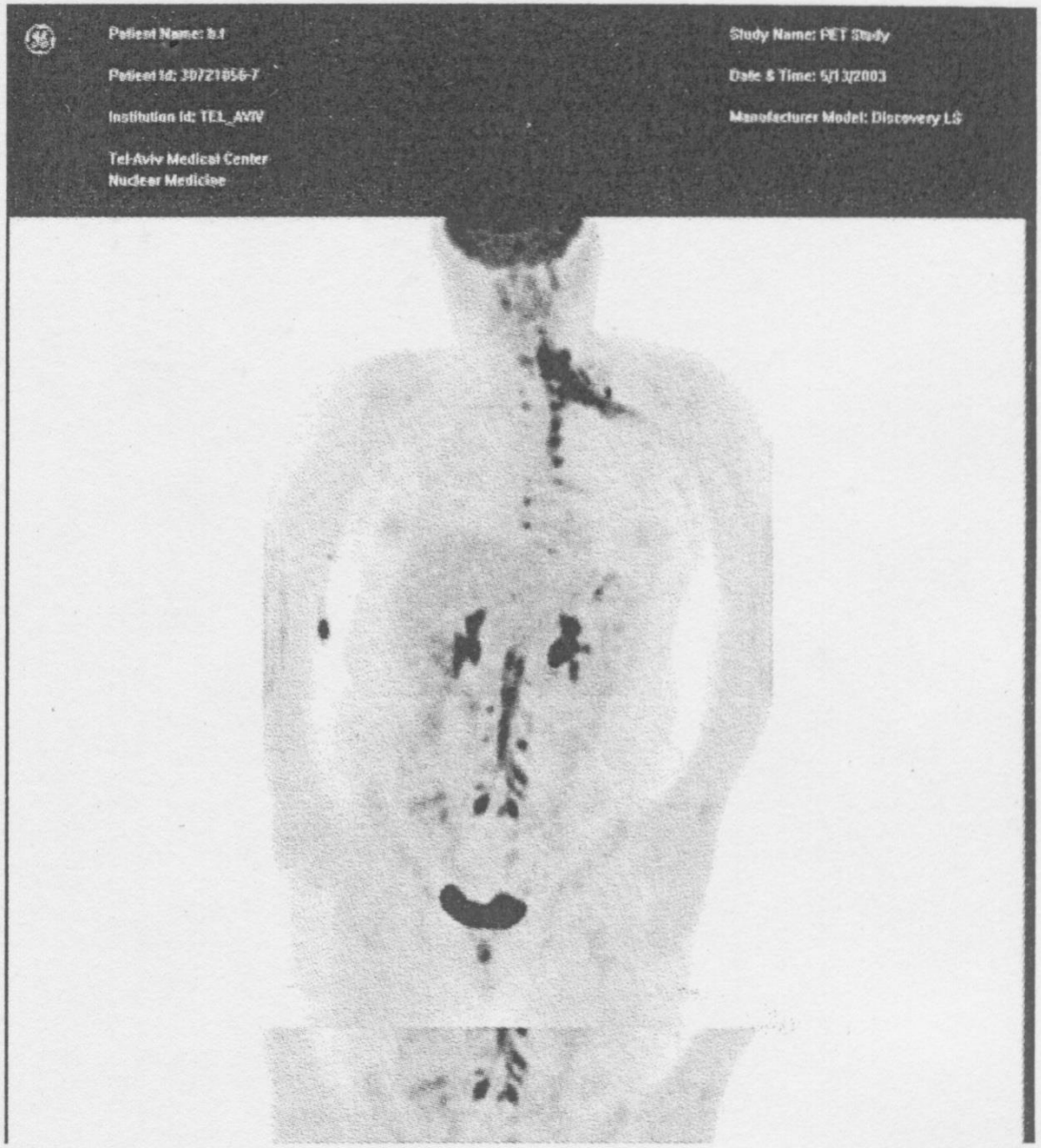
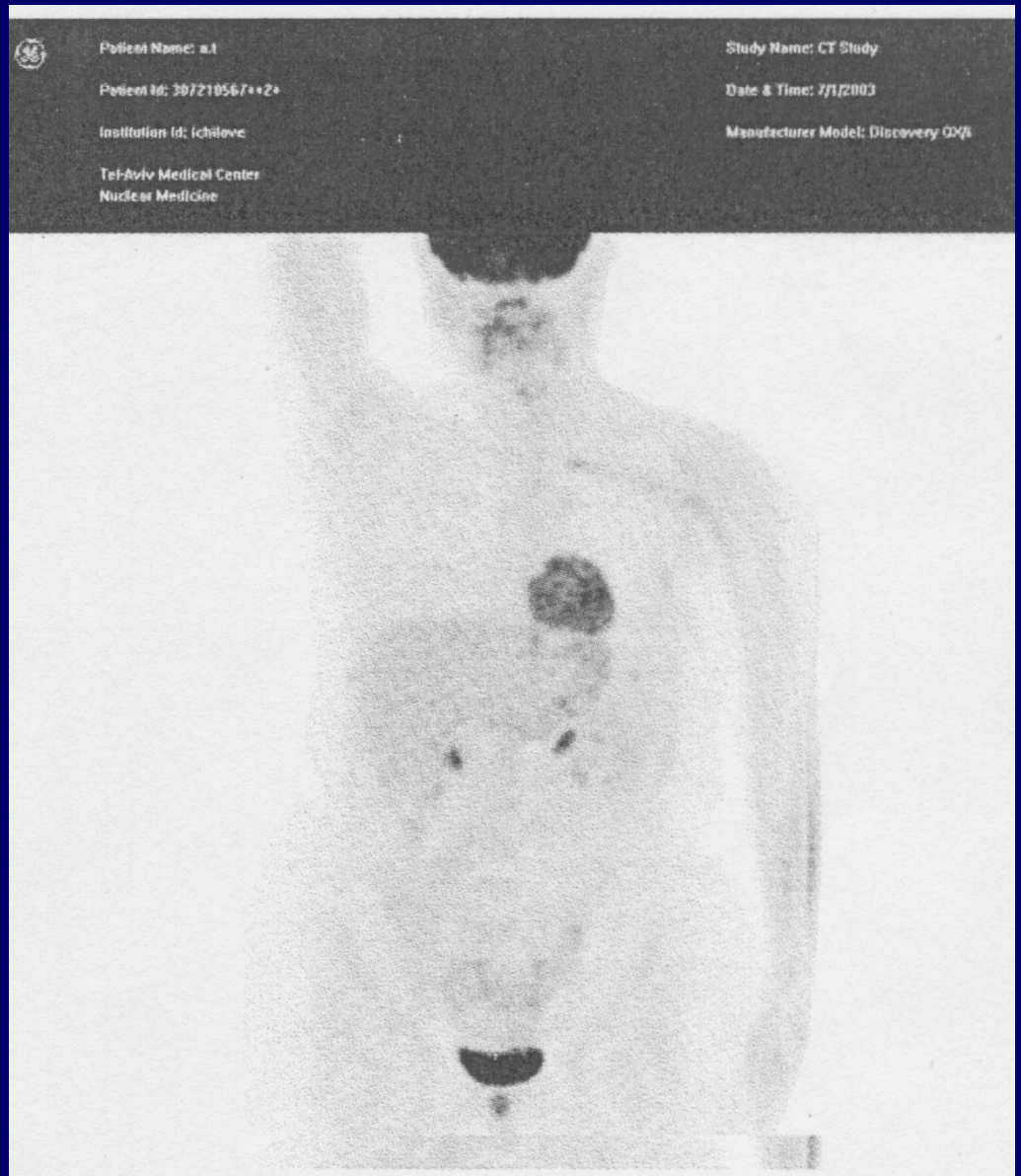


Caption 1: Image 1: Before



Caption 2: Image 2: After

Lymphomas

- Important to classify all NHL lymphomas according to:
  - the cell type
    - B and T cells
  - the grade of malignancy
- In case of low malignancy the tumour progresses slower, chemotherapy is less aggressive
- Lymphomas with high grade of malignancy have more aggressive course of disease and demand more active chemotherapy, the number of remissions is lower, prognosis poorer

TREATMENT

- The principles of NHL treatment depend upon the lymphoma's
  - histological type;
  - disease stage;
  - patient's age
- In cases of low malignancy lymphoma, stage I, the treatment can be limited to local radiation therapy, but the patient must be carefully examined prior to it (including immunohistochemistry of bone marrow and MRI) to exclude dissemination of the process.
- PET is the optimum method for specifying stage I

TREATMENT

- In all other cases of low malignancy NHL chemotherapy - COP or courses of CVP are used, Clorambutcil (Leukerani) or Cyclophosphamidi with /without using glycocorticosteroids, Fludara in combination with glucocorticoids or other cytostatic drugs
- Chemotherapy + Mabthera (Rituximab)
  - If CD-20+ lymphoma
- If the stage of lymphoma is already IV, and if the age of the patient and accompanying diseases allow it, CHOP course (+/- Mabthera) is most frequently used for treatment
- If autoimmune haemolytic anaemia has developed as a complication, then prolonged glucocorticoid therapy must be used.

TREATMENT

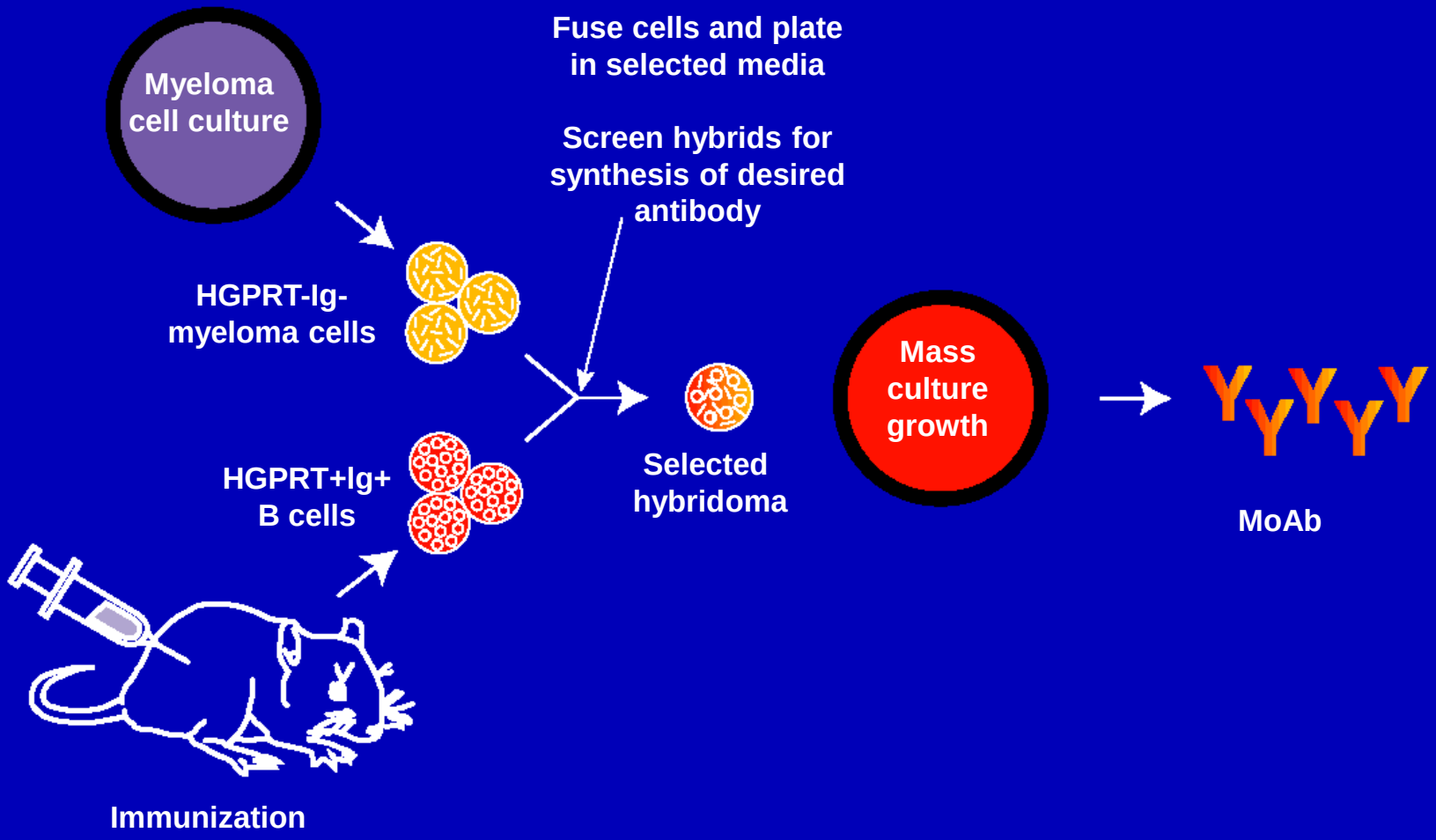
In cases of high malignancy NHL the treatment is more aggressive, usually – combined chemotherapy or high dose chemotherapy with following transplantation of bone marrow or peripheral blood stem cells.

- The most frequently used chemotherapy courses:
  - CHOP
  - m-BACOD
  - ProMACE-CytaBOM
  - MACOP-B
  - In recent years purine analogue Fludarabine is more frequently used to treat NHL, the most often used courses are
    - FMD (Fludarabine, Mitoxantrone, Dexamethasone),
    - Fludarabine and Cyclophosphamide.

Mabthera

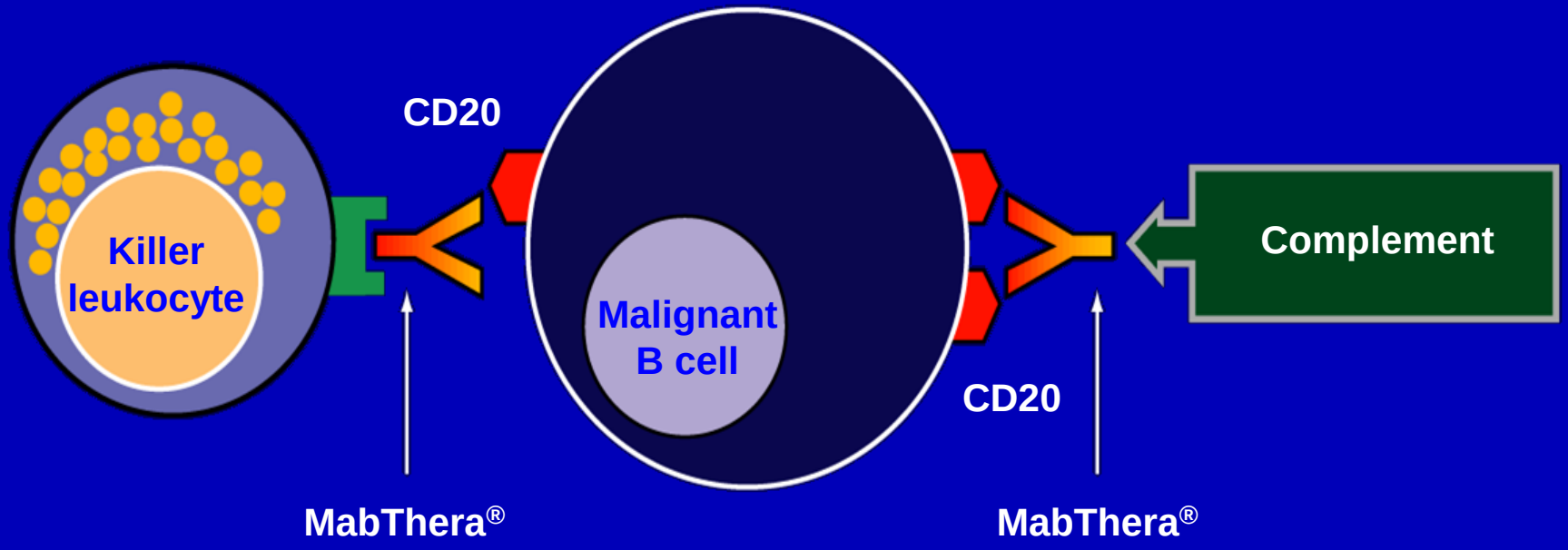
- Registered in the USA in December, 1997
- First registered indication - Non-Hodgkin's lymphoma
- At current Mabthera is used in the treatment of many diseases
  - Chronic lymphocytic leukaemia
  - Waldenström macroglobulinemia
  - Hodgkin's disease (lymphocyte predominance)
  - Lymphoproliferative disorders after transplantation
  - Different autoimmune disorders (ITP, autoimmune haemolysis, rheumatologic diseases)
  - Acute lymphoblastosis

Production of monoclonal antibodies



Adapted from Köhler et al. *Nature*. 1975;256:495.

MabThera and immune system cells interaction



Adapted from Male et al. *Advanced Immunology*. 1996;1:1.

Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte

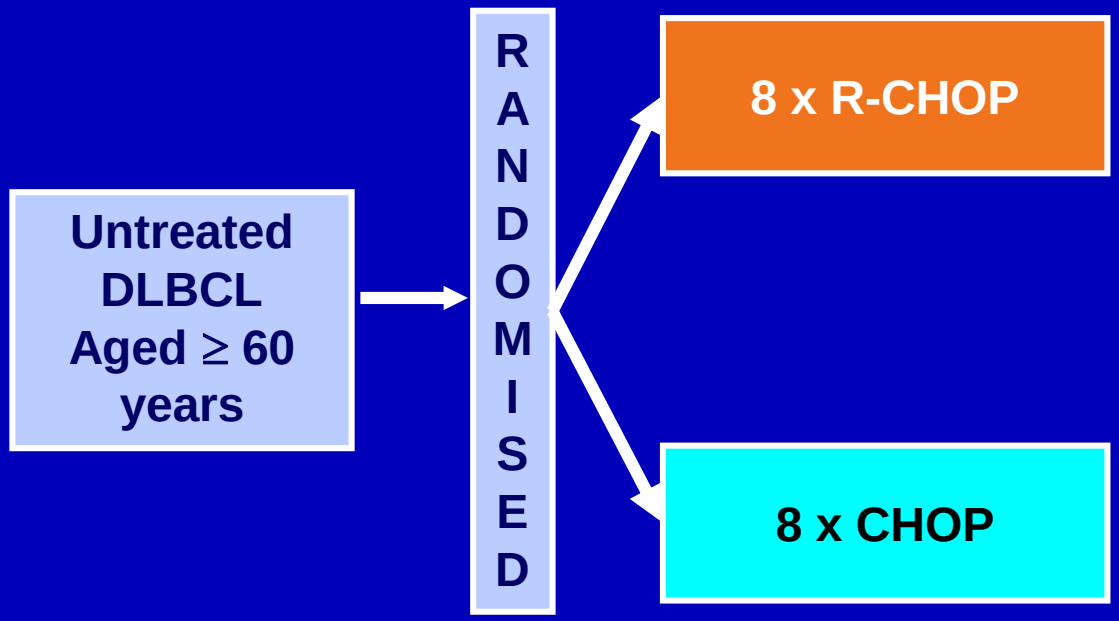
Coiffier B, Thieblemont C, Van Den Neste E, Lepeu G, Plantier I, Castaigne S, Lefort S, Marit G, Macro M, Sebban C, Belhadj K, Bordessoule D, Fermé C, Tilly H

Blood 2010; June 14 (epub ahead of print).

10 year long observation period for GELA LNH-98.5 research (R-CHOP vs CHOP in DLBCL):

- GELA LNH-98.5 research compared R-CHOP as first line standard treatment protocol in case of diffuse large B-cell lymphomas (DLBCL)
- In year 2000 in American Hematological Congress for the first time the data was reported, which in the last more than 25 years for the first time showed an increase of overall survival of elderly patients with DLBCL
- 10 year analysis shows, that preponderance of R-CHOP to CHOP persists over time, in both low and high risk patient groups

GELA LNH-98.5: design of the research



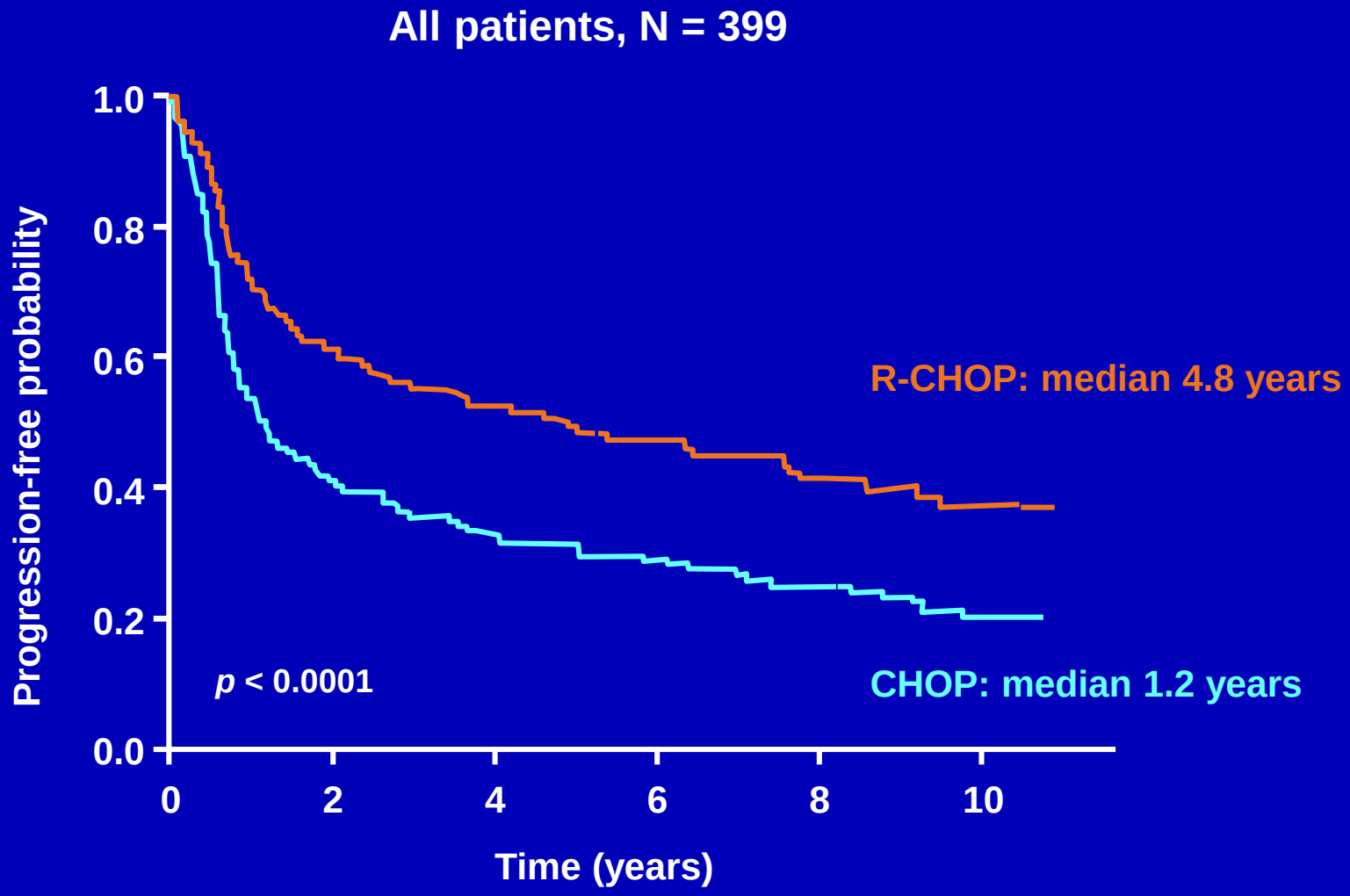
CHOP: Cyclophosphamide 750 mg/m²
Doxorubicin 50 mg/m²
Vincristine 1.4 mg/m²
Prednisone 40 mg/m²/day x 5 days

R-CHOP: MabThera 375 mg/m² Day 1 of each cycle

Cycles every 21 days

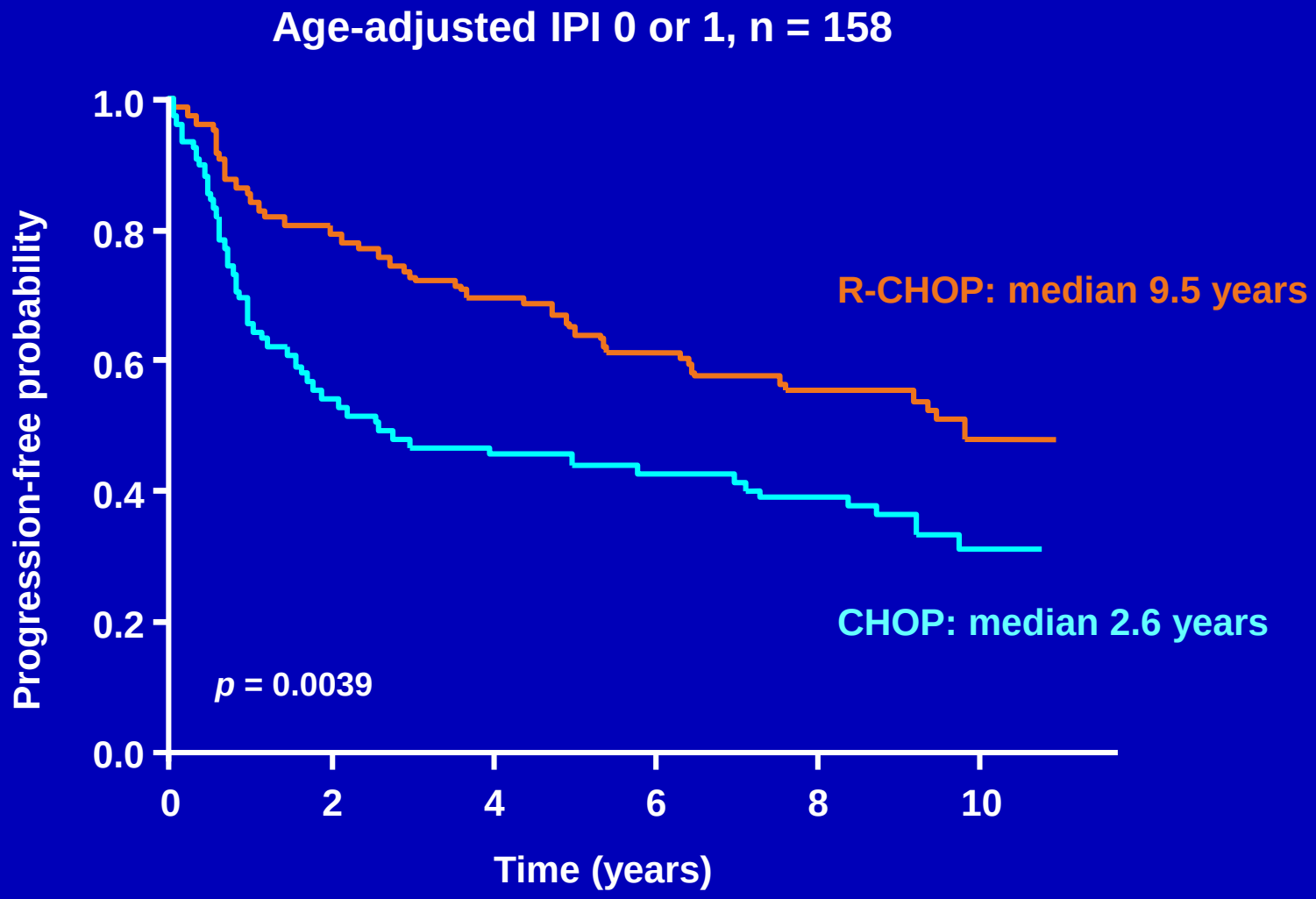
Coiffier B, *et al. Blood* 2010; June 14: (epub ahead of print).

GELA LNH-98.5 10 year observation results: survival without tumor progression



Coiffier B, *et al. Blood* 2010; June 14: (epub ahead of print).

GELA LNH-98.5 10 year observation results: survival without tumor progression of low risk patients



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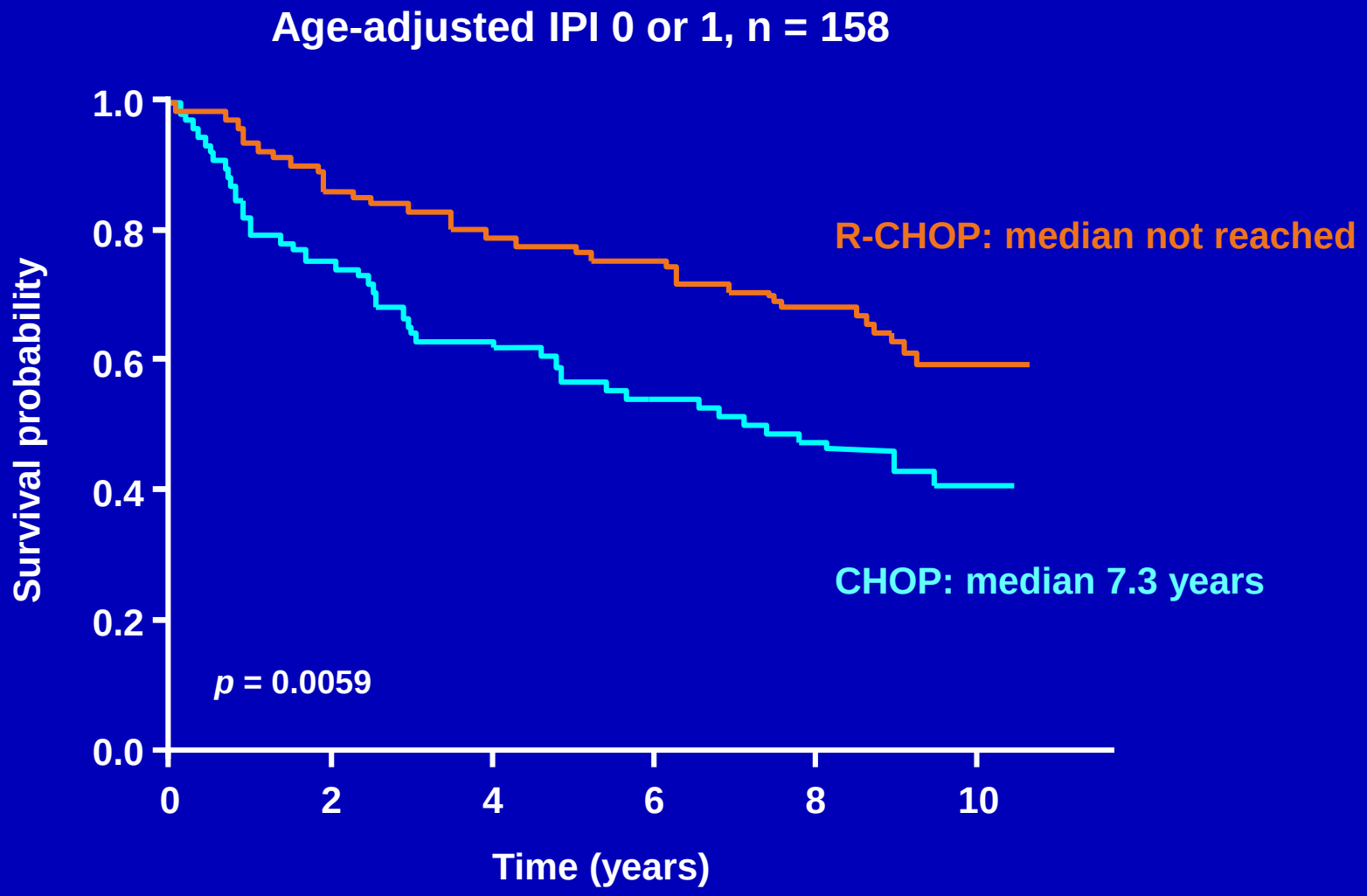
GELA LNH-98.5 10 year observation results: survival of low risk patients



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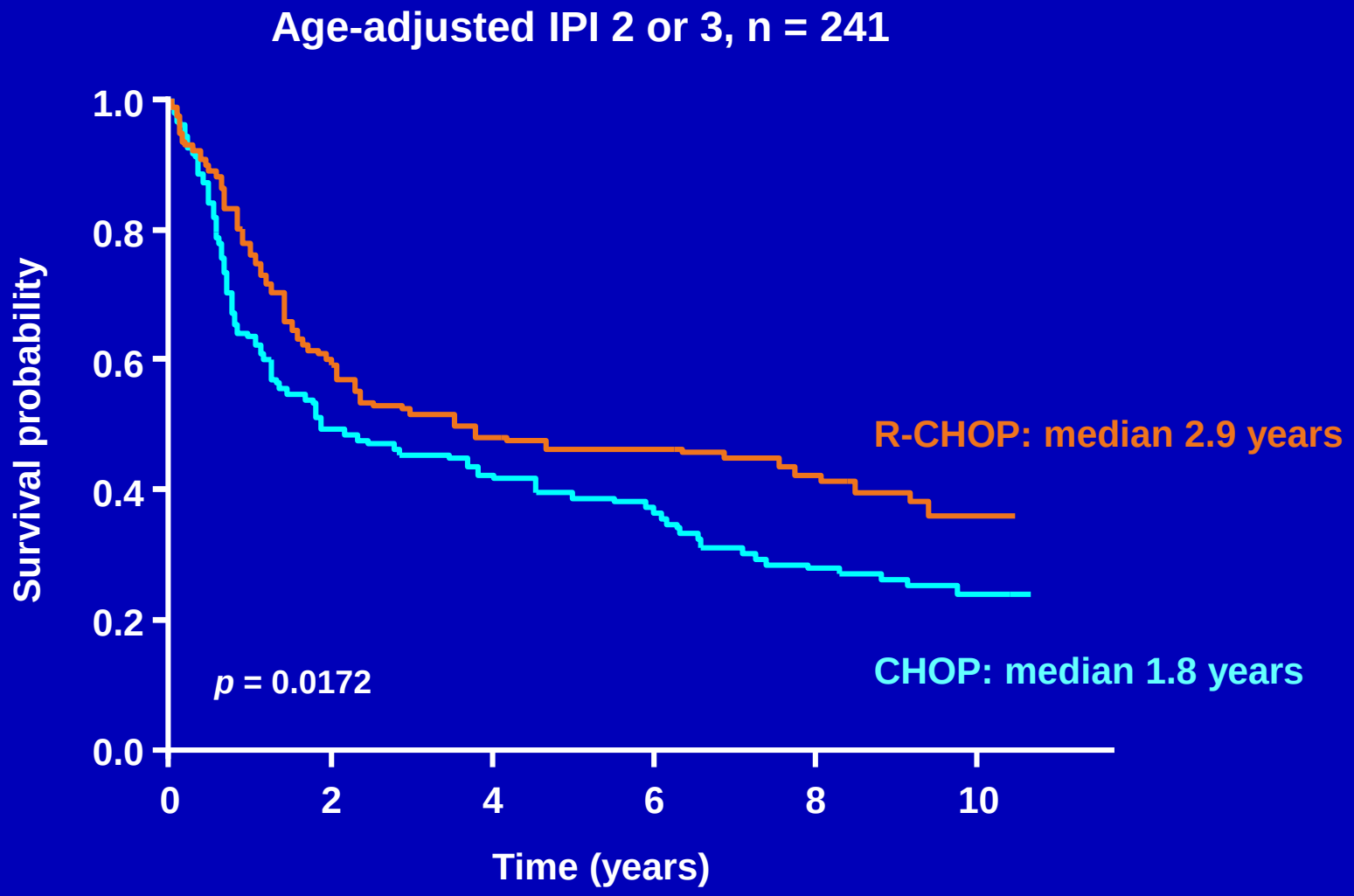
GELA LNH-98.5 10 year observation results: survival of high risk patients



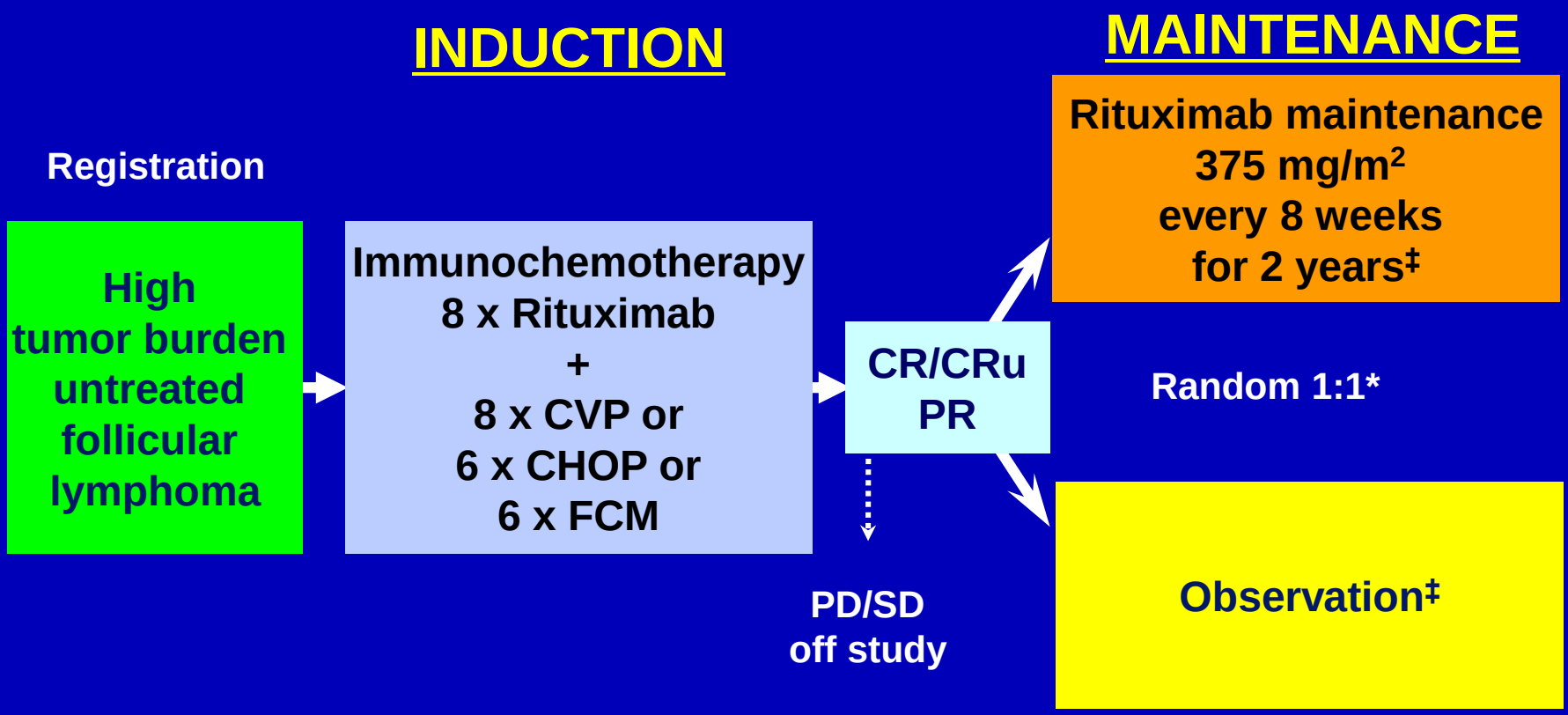
Coiffier B, *et al. Blood* 2010; June 14: (epub ahead of print).

Rituximab Maintenance for 2 Years in Patients with Untreated High Tumor Burden Follicular Lymphoma After Response to Immunochemotherapy

G. A. Salles, J. F. Seymour, P. Feugier, F. Offner, A. Lopez-Guillermo, R. Bouabdallah, L. M. Pedersen, P. Brice, D. Belada, L. Xerri on behalf of the PRIMA investigators

Gilles Salles
Hospices Civils de Lyon
& Université Claude Bernard, Lyon, France

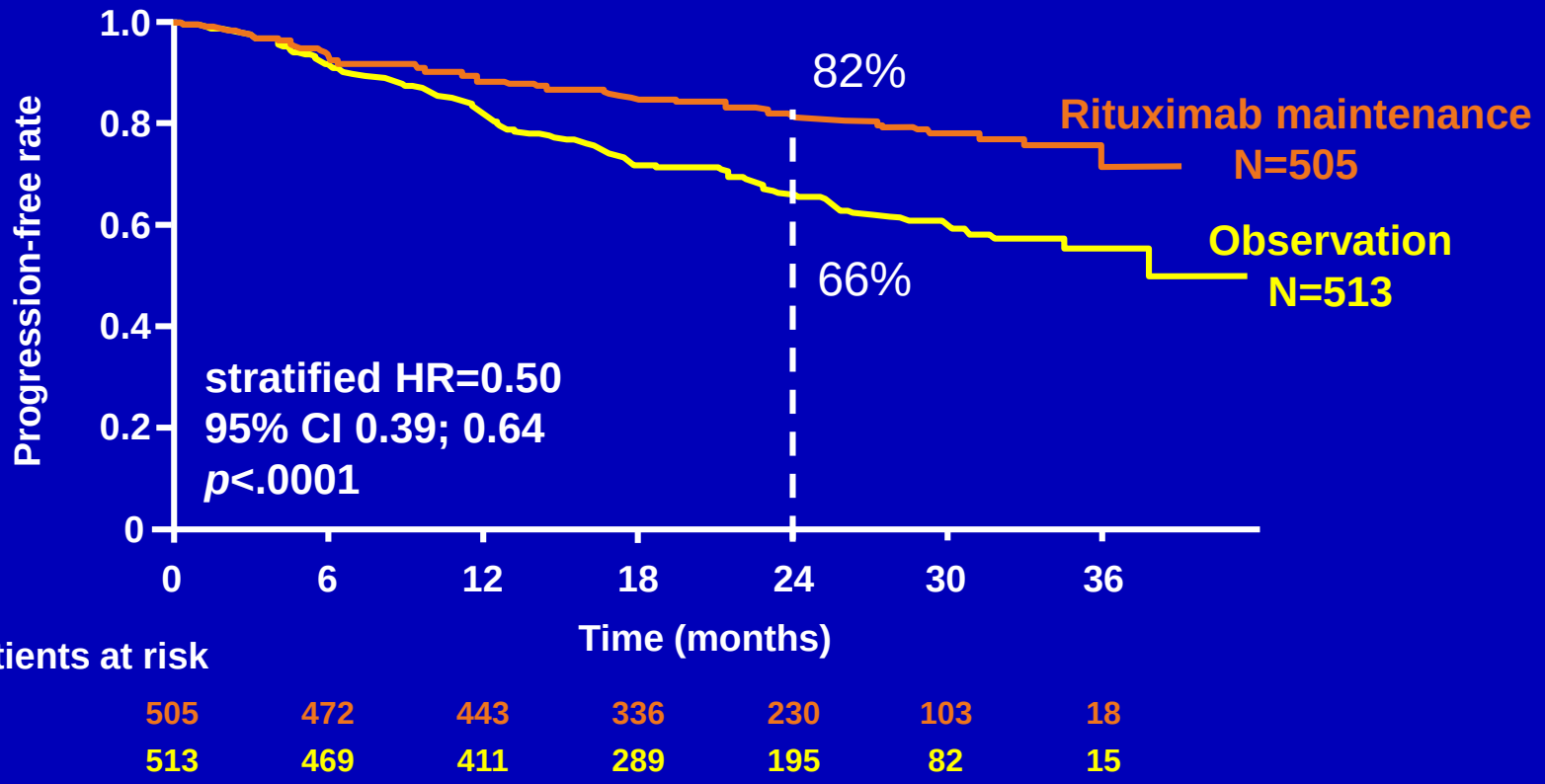
PRIMA: study design



* Stratified by response after induction, regimen of chemo, and geographic region
‡ Frequency of clinical, biological and CT-scan assessments identical in both arms
Five additional years of follow-up

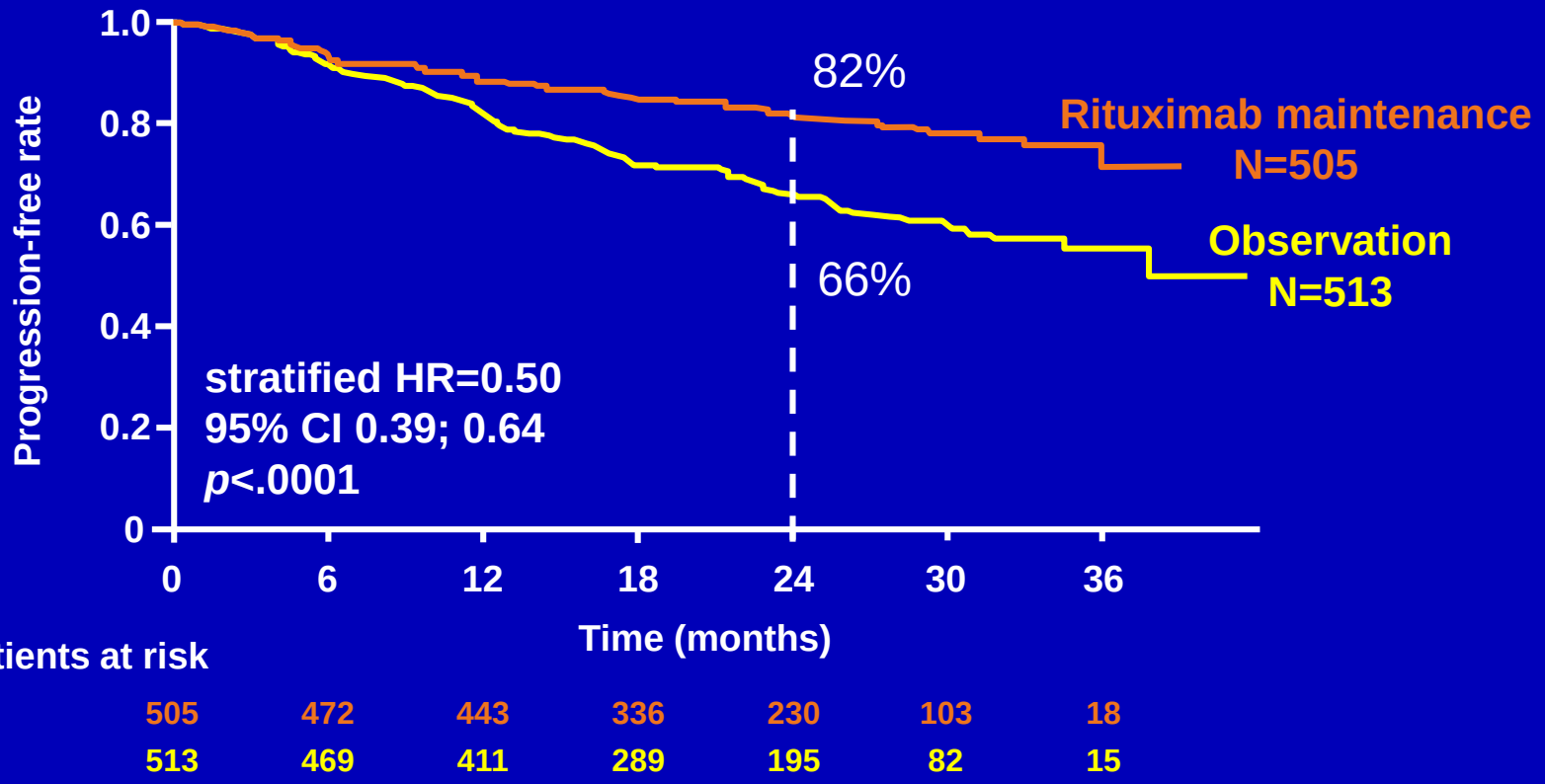
Primary endpoint (PFS) met at the planned interim analysis

Rituximab maintenance significantly reduced the risk of progression by 50%



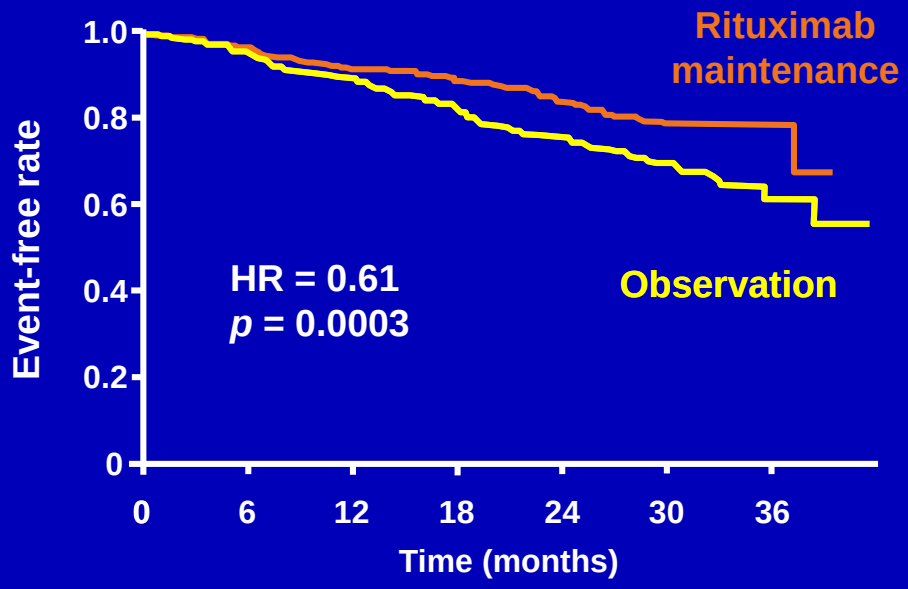
First goal - to determine the progression

Rituximab maintenance significantly reduced the risk of progression by 50%



Time until next therapy

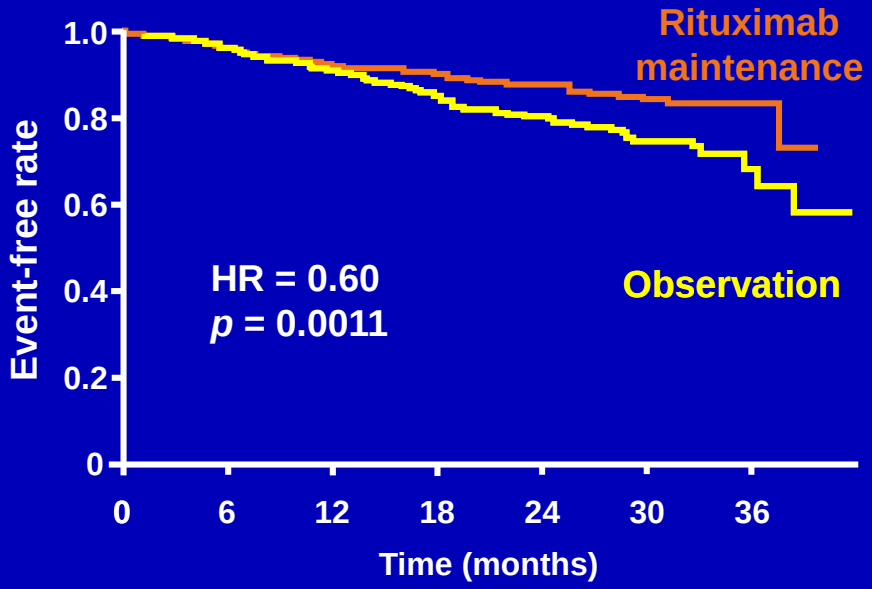
Time to next anti-lymphoma treatment



Patients at risk

Rituximab maintenance	505	483	453	349	235	103	18
Observation	513	487	447	327	218	87	15

Time to next chemotherapy treatment



Rituximab maintenance	505	484	457	351	243	108	19
Observation	513	492	454	332	225	91	17

Conclusions

- The addition of monoclonal antibodies to CHOP course significantly improves treatment results, which is testified by patient observation over a period of 10 years
- Mabthera currently is used in low and high malignancy stages, CD-20+ lymphoma cases, and also in case of chronic lympholeucosis
- Mabthera introduced a new era in tumour therapy - immunochemotherapy

TREATMENT

- If a relapse of high malignancy lymphomas is observed or if resistance against poly-chemotherapy is observed, either the so-called "salvage" chemotherapy courses or high dose chemotherapy must be used with following transplantation of autologous stem cells.
- "Salvage" chemotherapy courses are MIME, MINE, ICE, DHAP, which comprise such drugs as Ifosfamide, Metotrexate, Cytarabine, Cisplatin, Etoposide
- Currently data on transplantation of allogenous bone marrow or peripheral blood stem cells are also available

Lymphoma evaluation

- Stage
- CR – complete remission
- PR – partial remission/ response
- PD – progressive disease
- R – relapse (early – during the first year of remission; late – after 1 year)

PROGNOSIS

- Prognosis can be very different, it depends upon:
  - histological type of NHL
  - stage of the disease
  - patient's age
  - clinical conditions
  - accompanying diseases, which can limit the possibilities of poly-chemotherapy.
- In general 65-69% of patients have 5 years survival rate
- With improving treatment possibilities, the life expectancy of patients increases

Extranodal lymphomas

Primary extranodal lymphomas

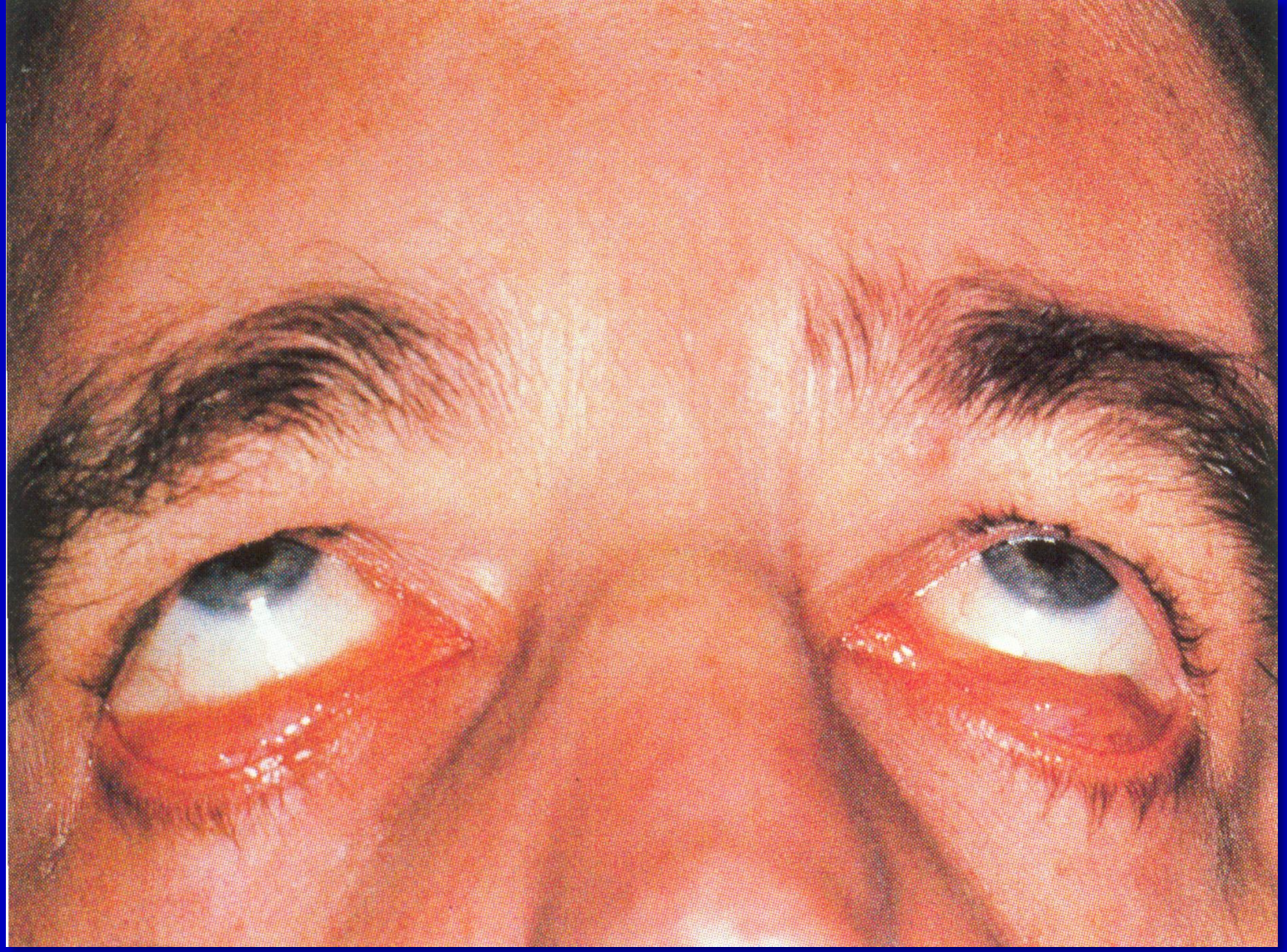
- Typically lymphoma primary originates in the lymph node, but more and more primary localizations are outside the lymph nodes
  - Stomach
  - Skin
  - Eyes, orbit
  - Bone lymphomas
  - Breast
  - CNS
  - Thyroid gland
  - Root of the tongue

Primary extranodal lymphomas

- Gastric and intestinal canal
  - Most common extranodal localization (4-20%)
  - In Western countries dominant are gastric lymphomas, in Eastern countries - intestinal lymphomas
  - Currently gastrectomy is not used as first line measure, start with chemotherapy or radiation
  - Paranasal sinuses
  - Most common B-cell high malignancy level

Primary extranodal lymphomas

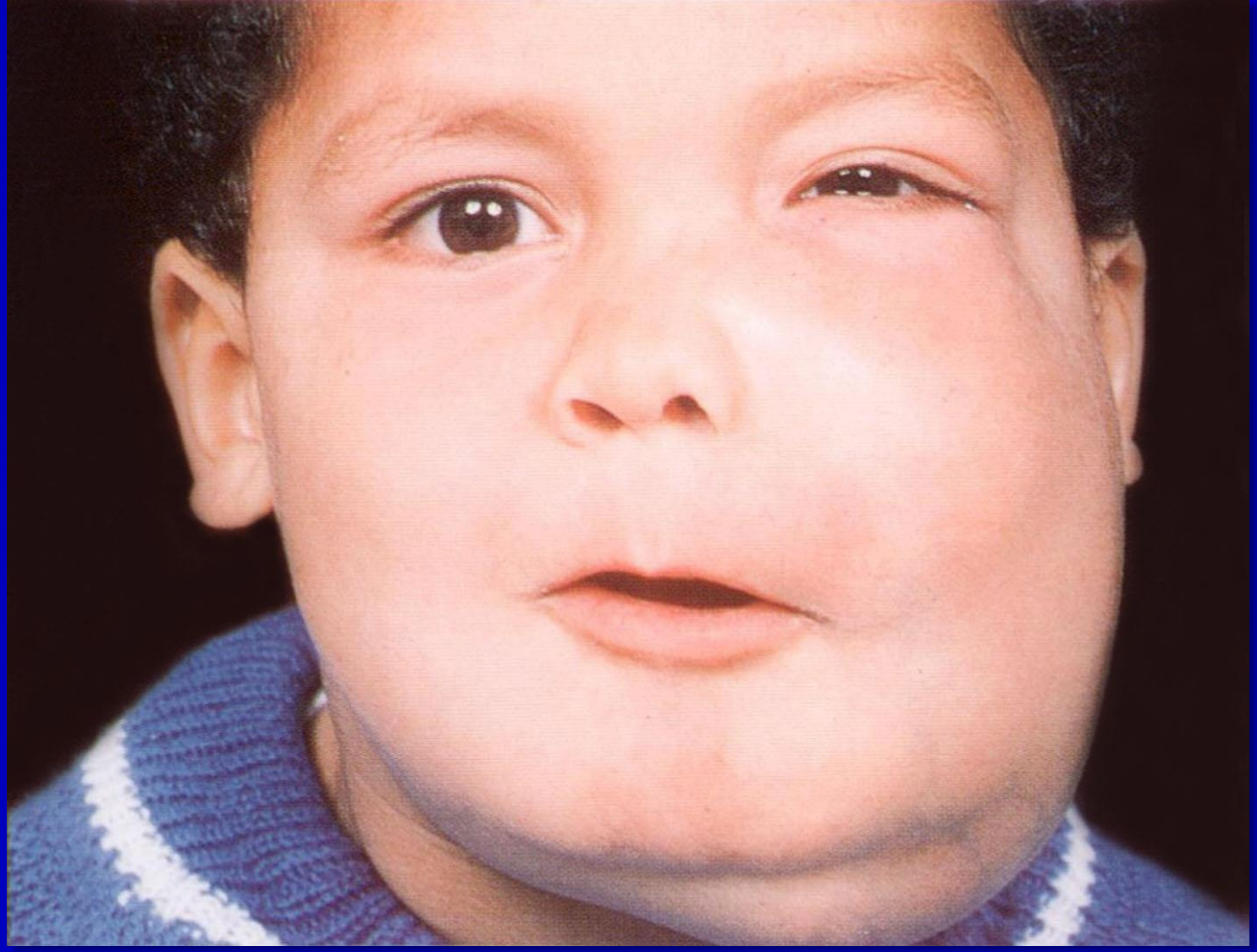
- Eye, orbit lymphomas
  - Remind of inflammation process
- Primary spleen lymphomas
  - Most recently as focal changes in the spleen
- Primary thyroid gland lymphomas
  - 2-3% from all extranodal lymphomas
  - 2-8% from this localizations malignant tumours



Lymphoma of eye-lids

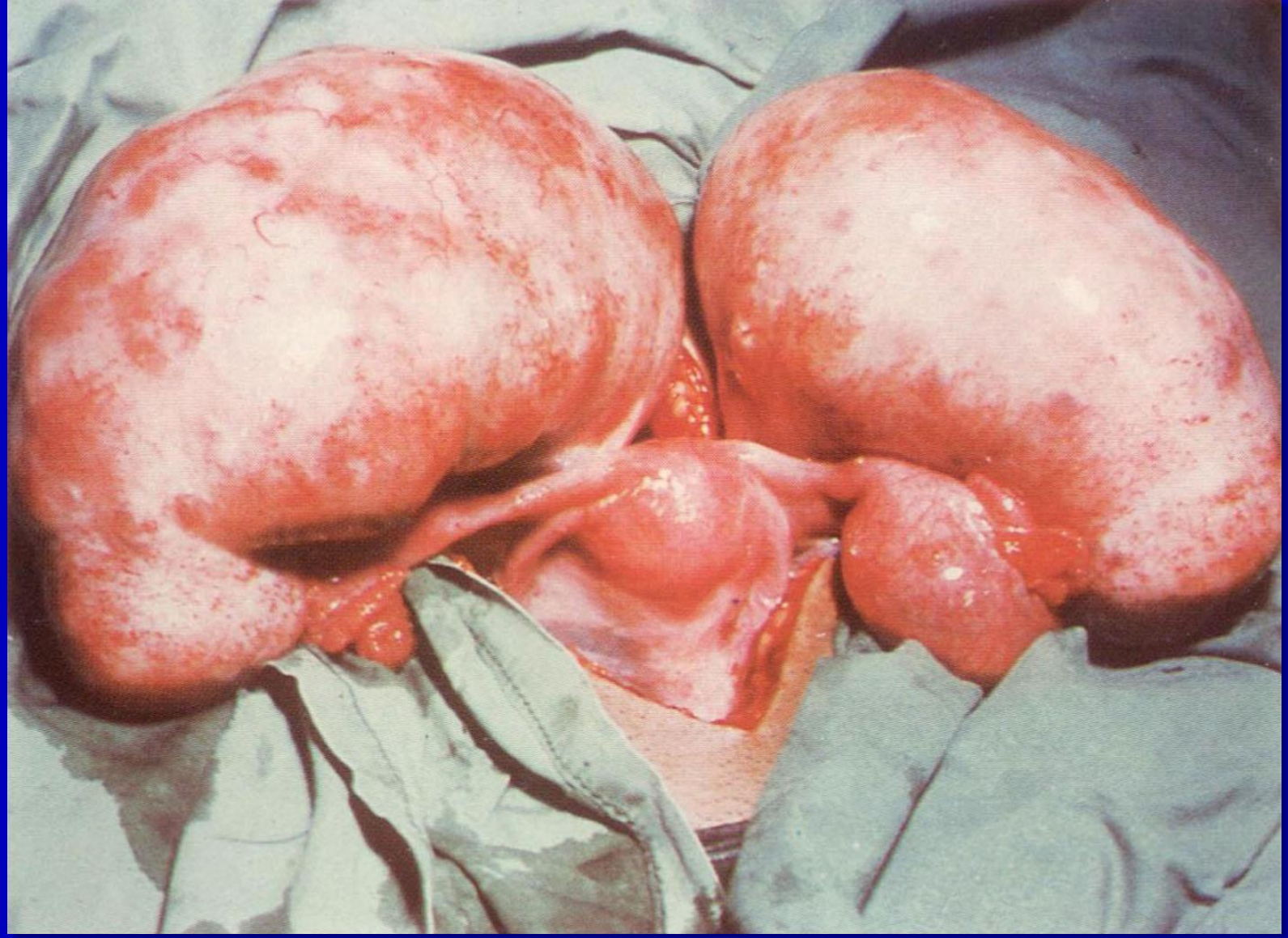
Primary extranodal lymphomas

- Skin lymphomas
  - Uncertain skin formations
- Primary bone lymphomas
  - Often also pathologic bone fracture
- Primary liver lymphomas
  - Very rare – 0.4% from extranodal lymphomas



Burkitt's lymphoma. Tumor from the lymph node also infiltrated the mandible and soft tissues.

«Clinical Haematology» 1994/A. Victor Hoffbrand, John E. Pettit



Burkitt's lymphoma. Bilateral ovarian infiltration.

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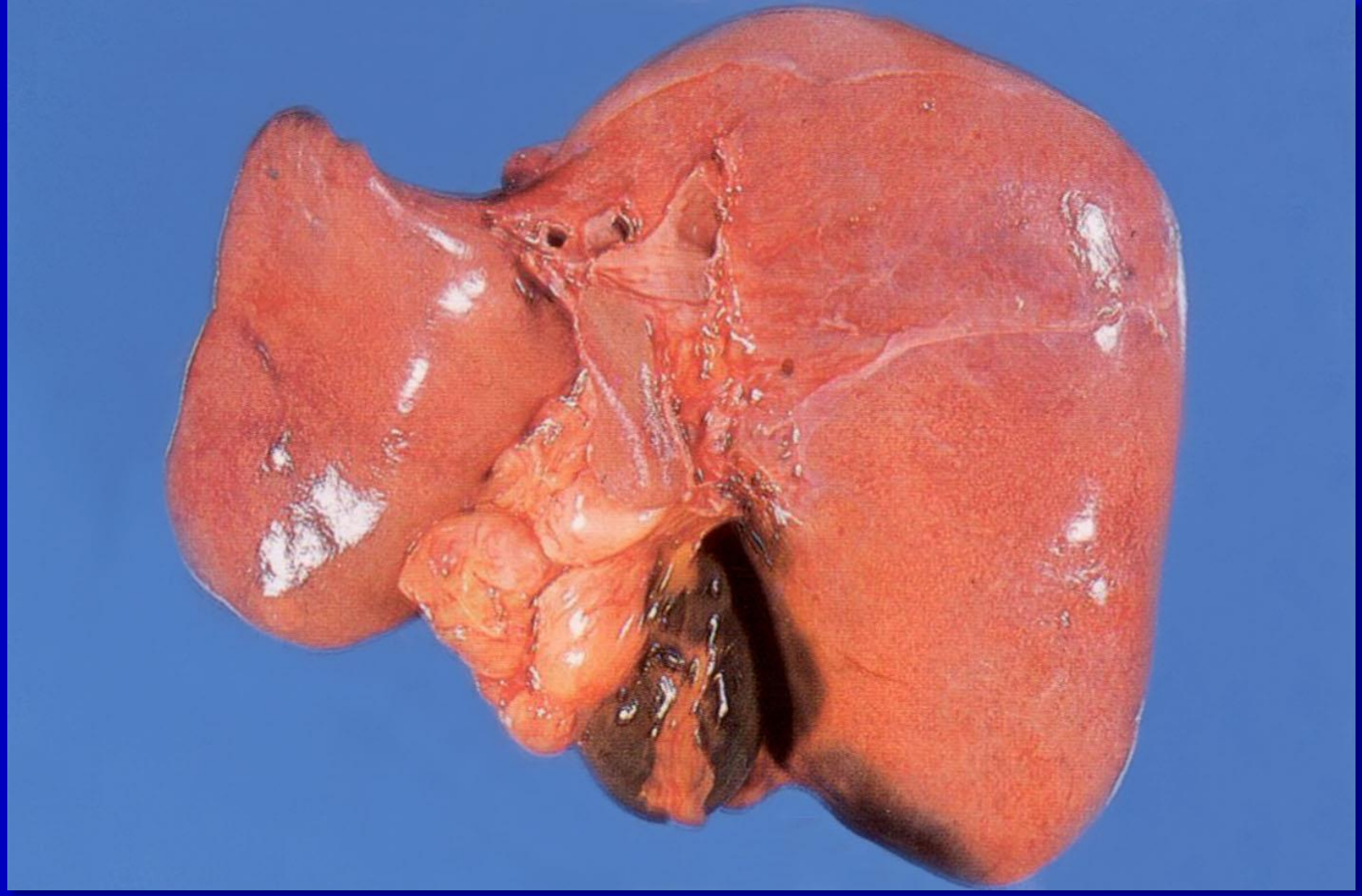

Non-Hodgkin's lymphoma. Lymphadenopathy in portal fissure.

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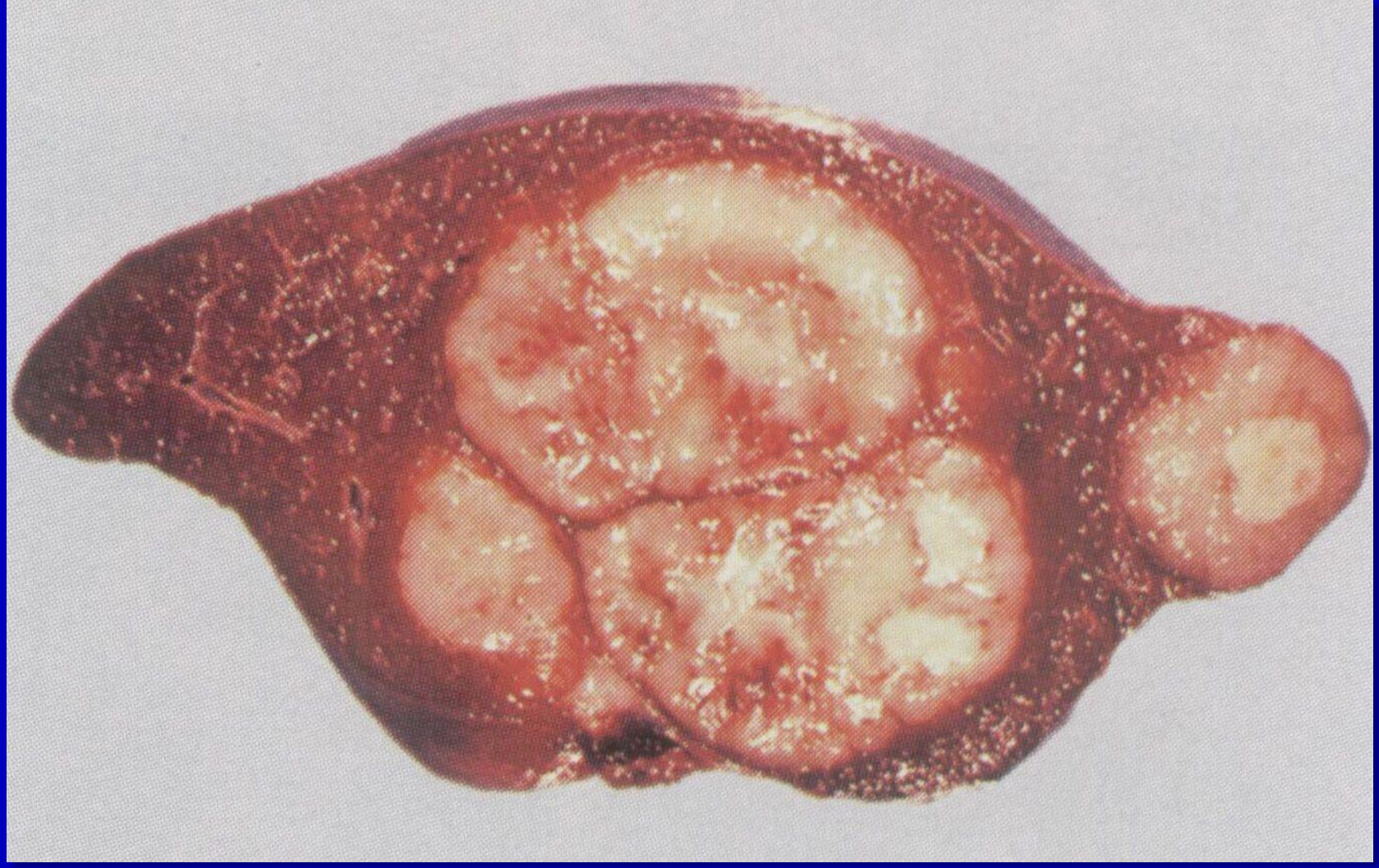
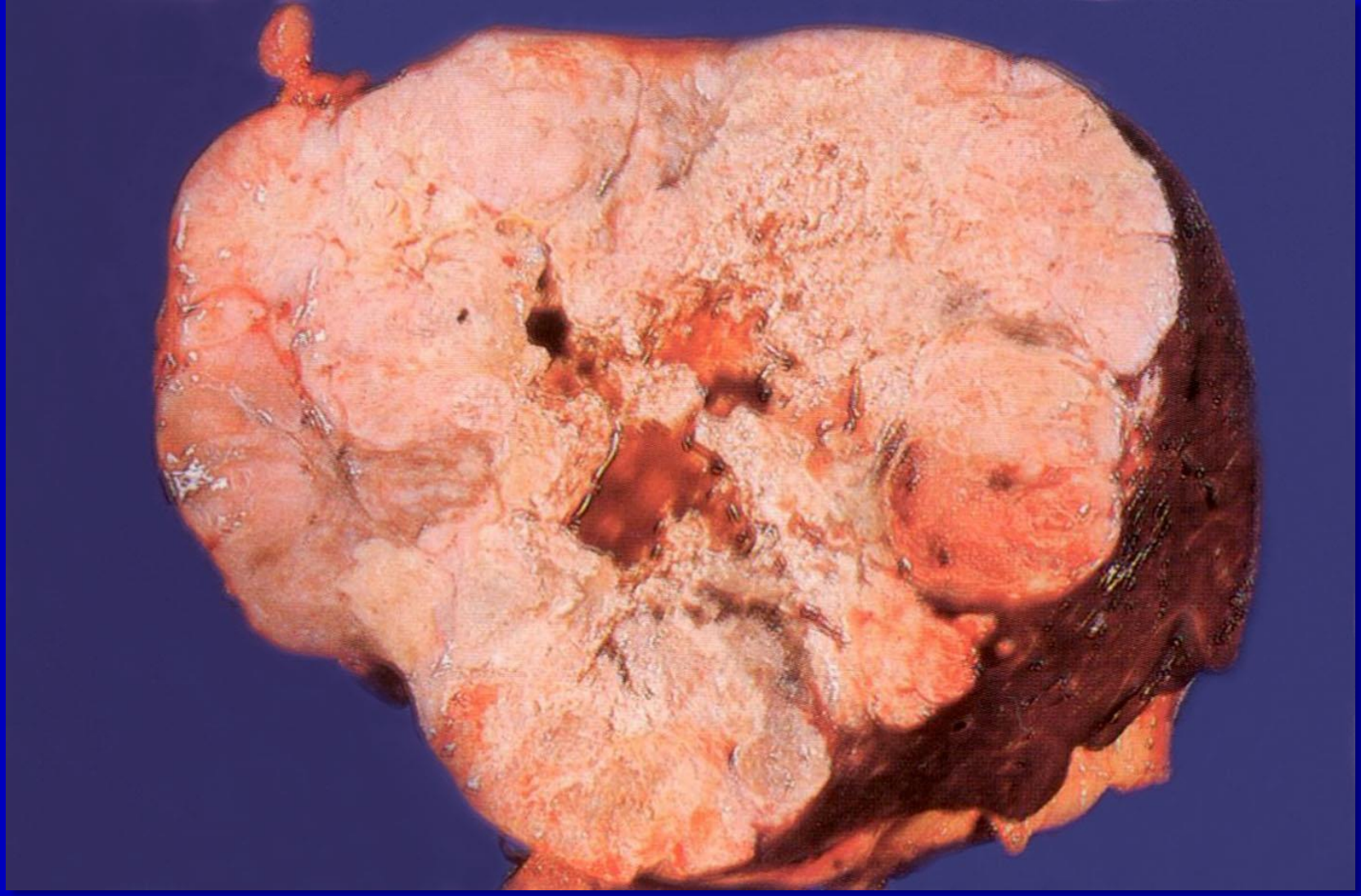


Lymphoma in liver



Non-Hodgkin's lymphoma. Spleen, after splenectomy.

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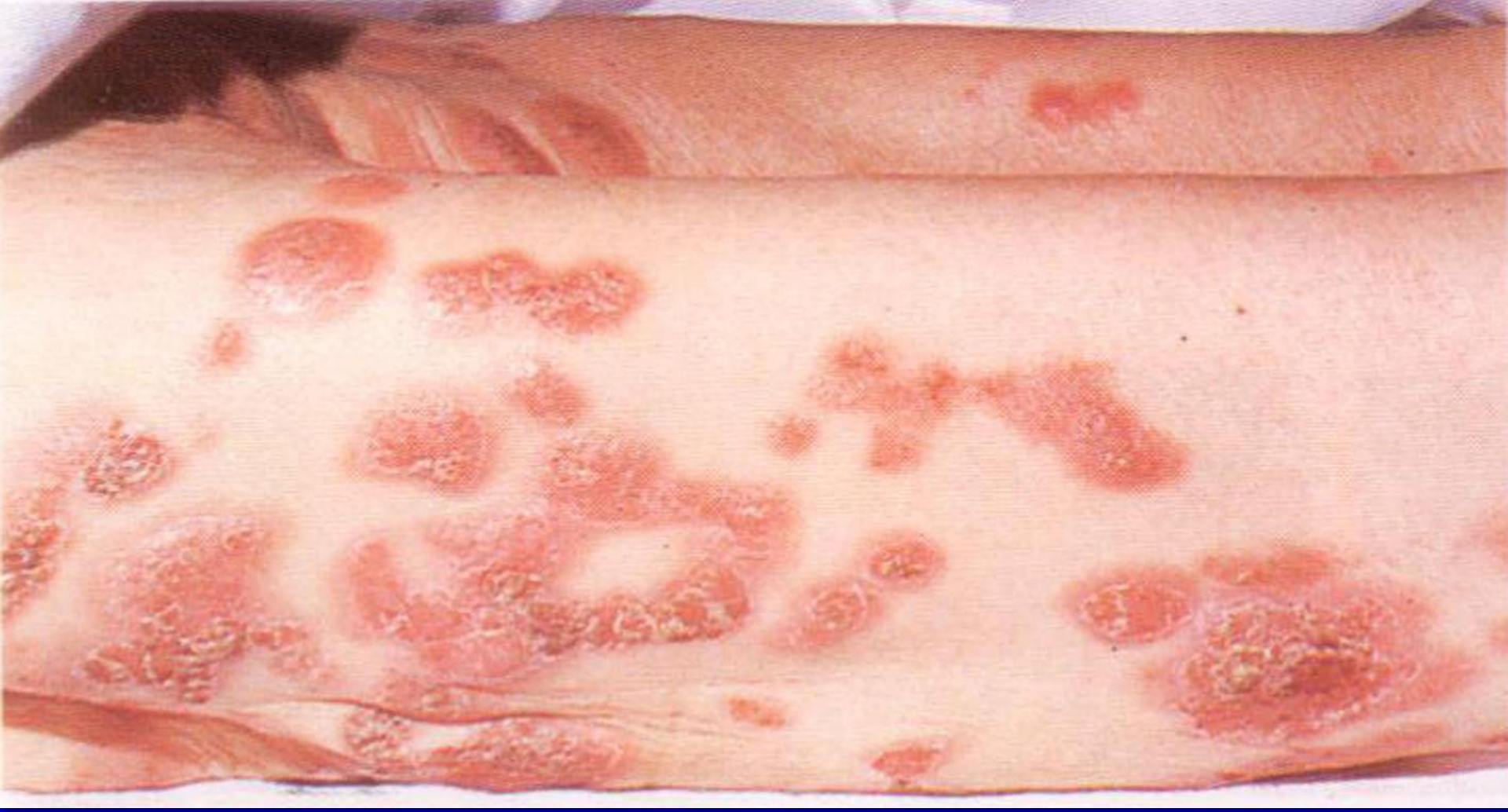
Skin lymphomas



Non-Hodgkin's lymphoma, centroblastic lymphoma.
Skin specific infiltration.

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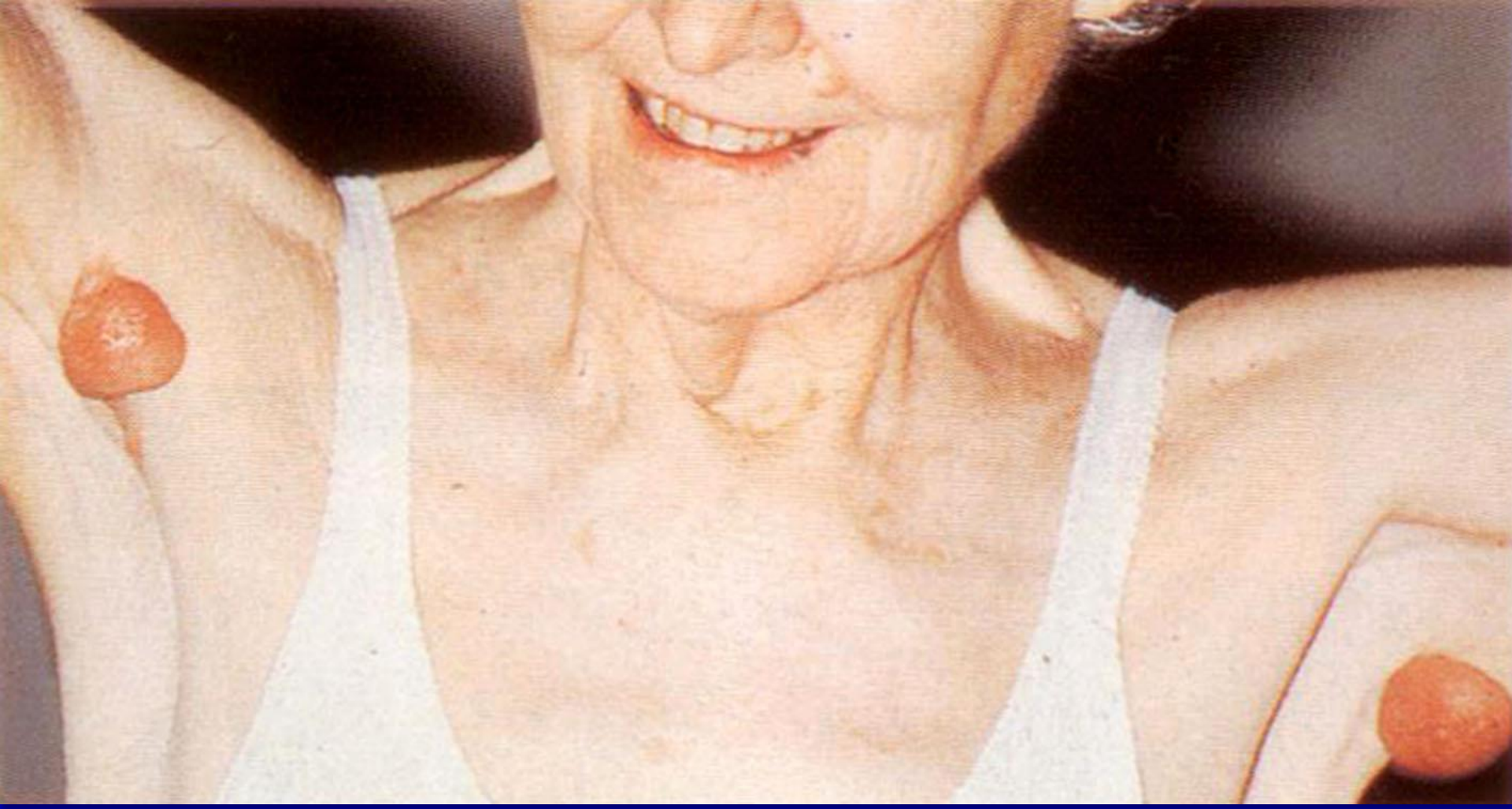

Non-Hodgkin's lymphoma, centrocytic/centroblastic.
Specific skin deposits.

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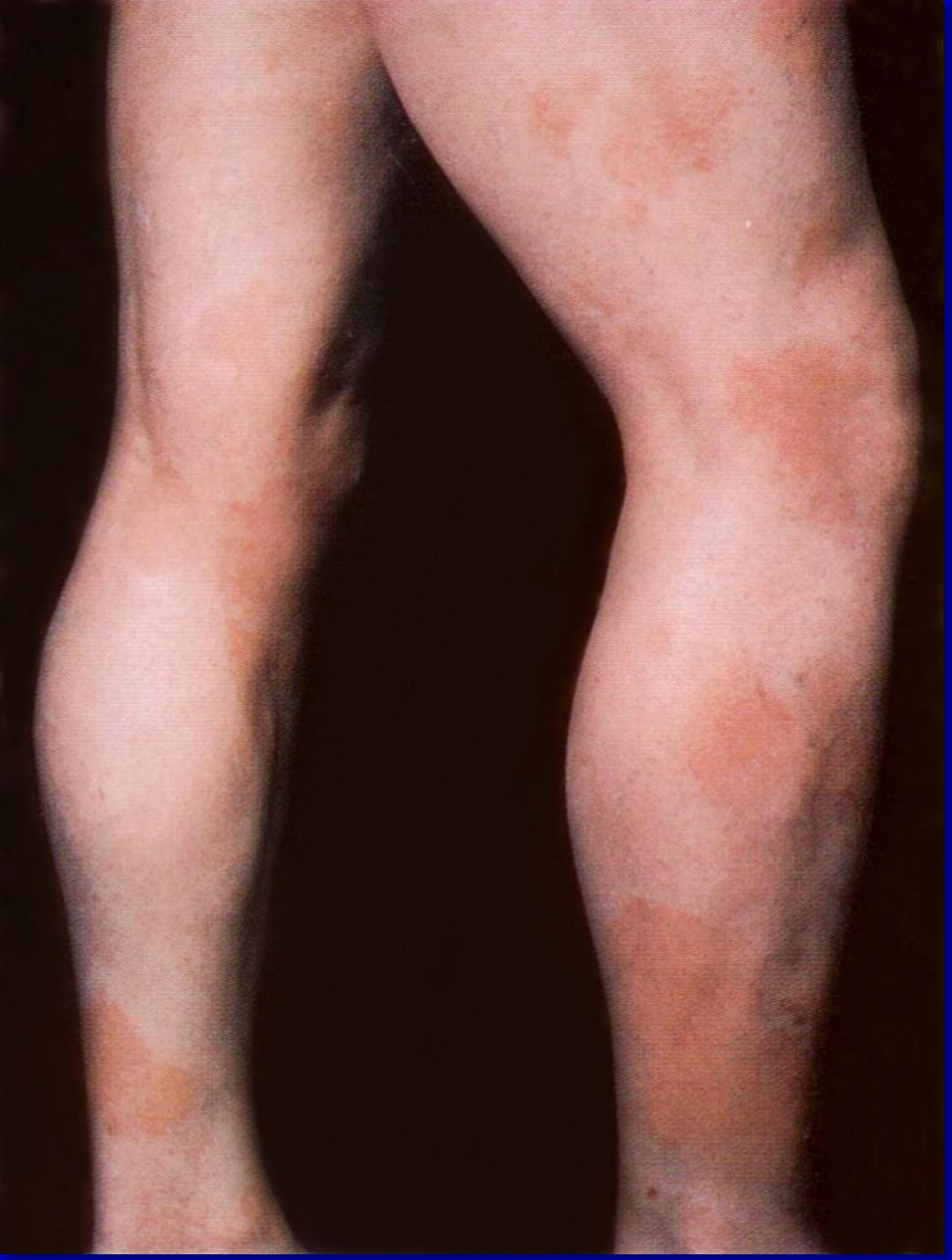

NHL. Mycosis fungoides. Erythematous skin damage.

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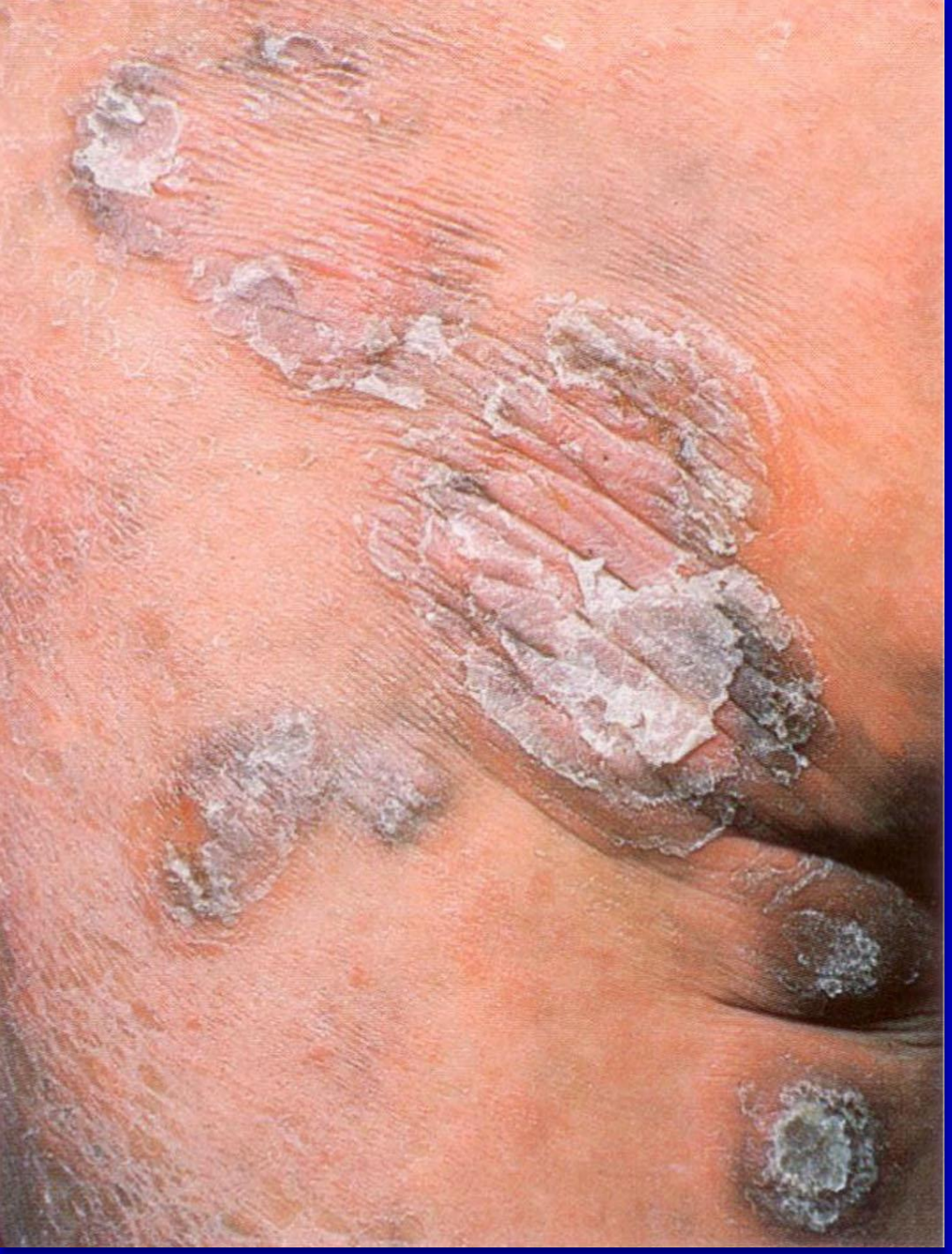

Mycosis fungoides. Skin desquamation, similar to psoriasis.

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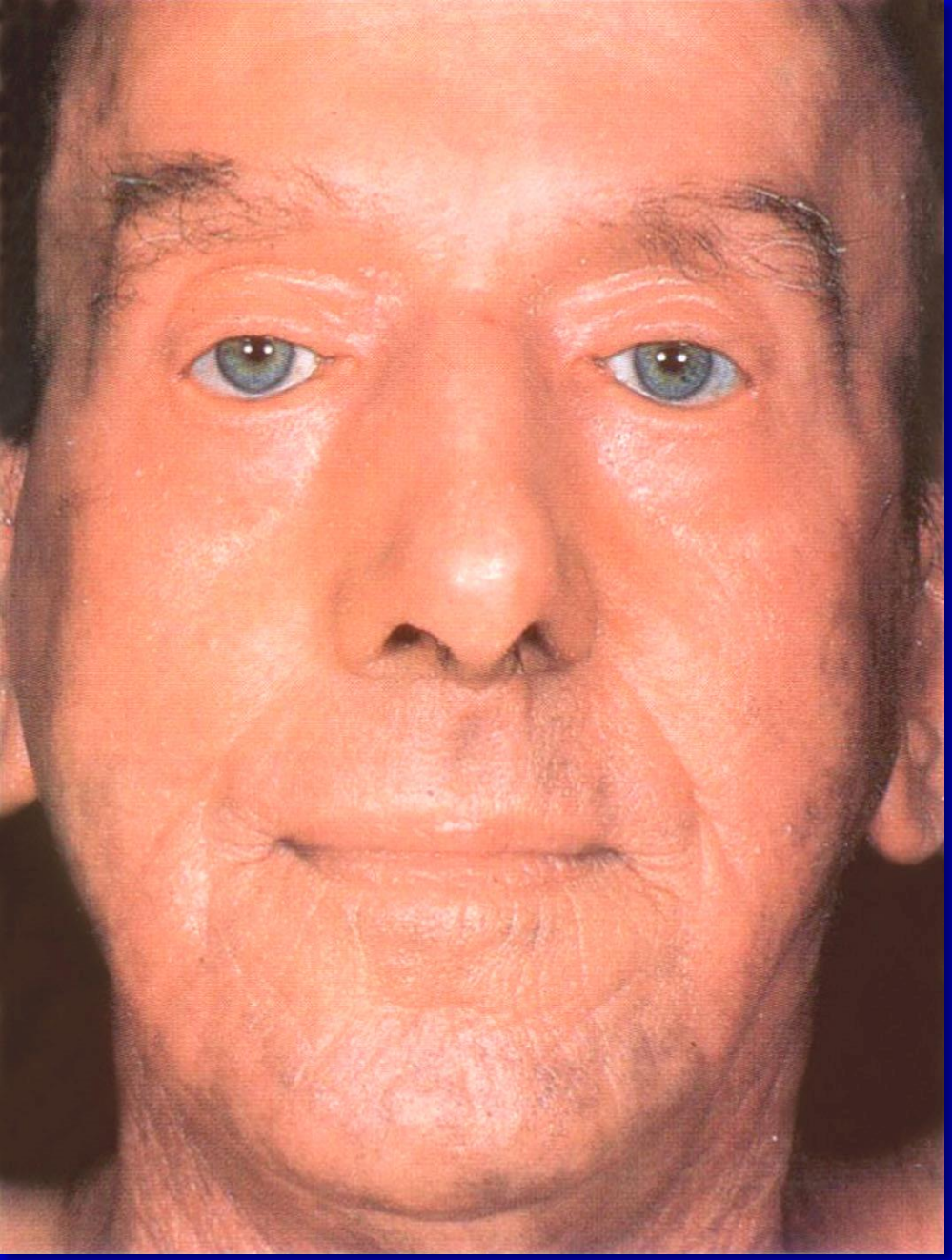
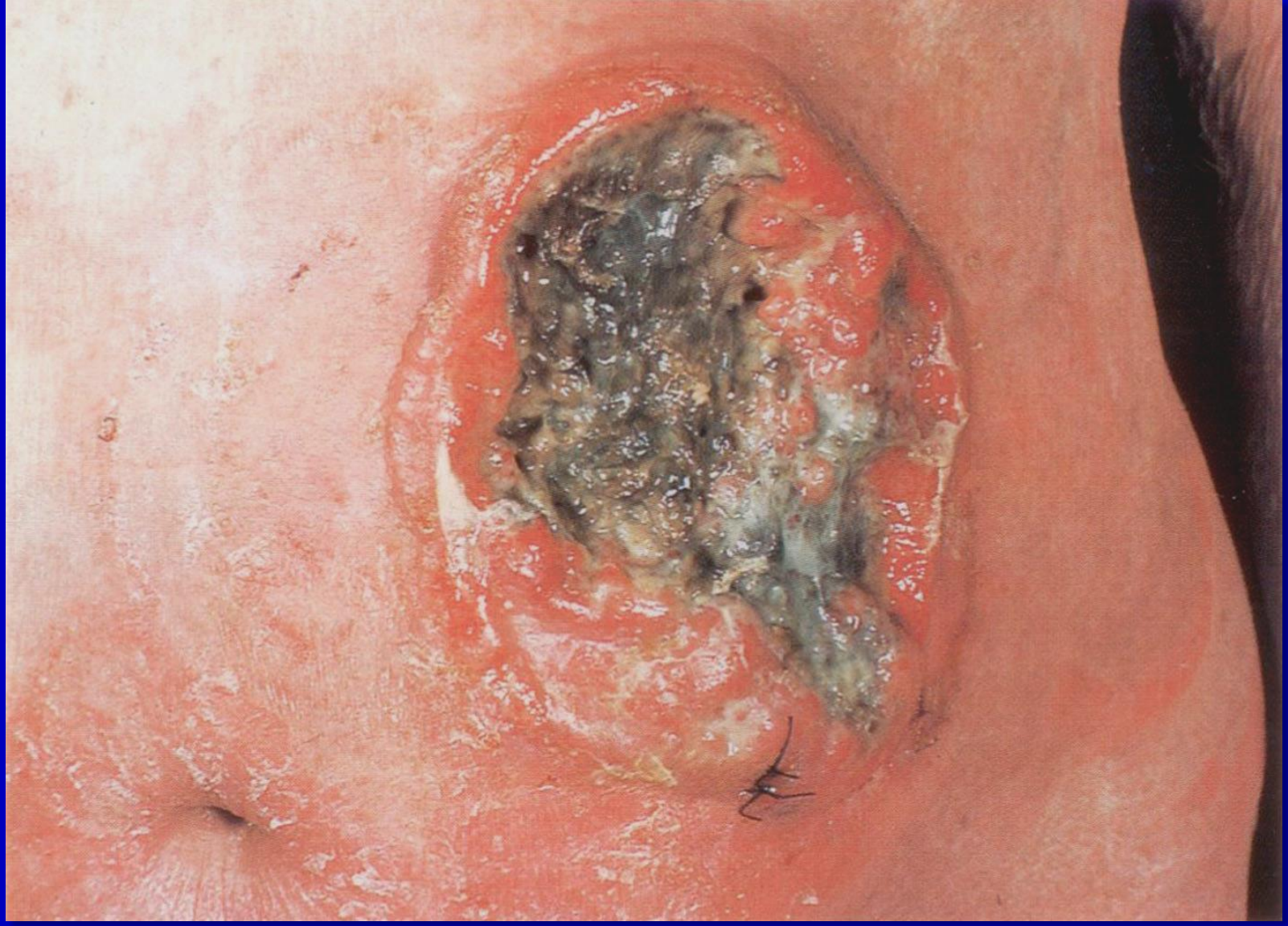


Mycosis fungoides. Erythroderma.

«Clinical Haematology» 1994/A. Victor Hoffbrand, John E. Pettit



Mycosis fungoides. Ulcer in invasive tumor case.

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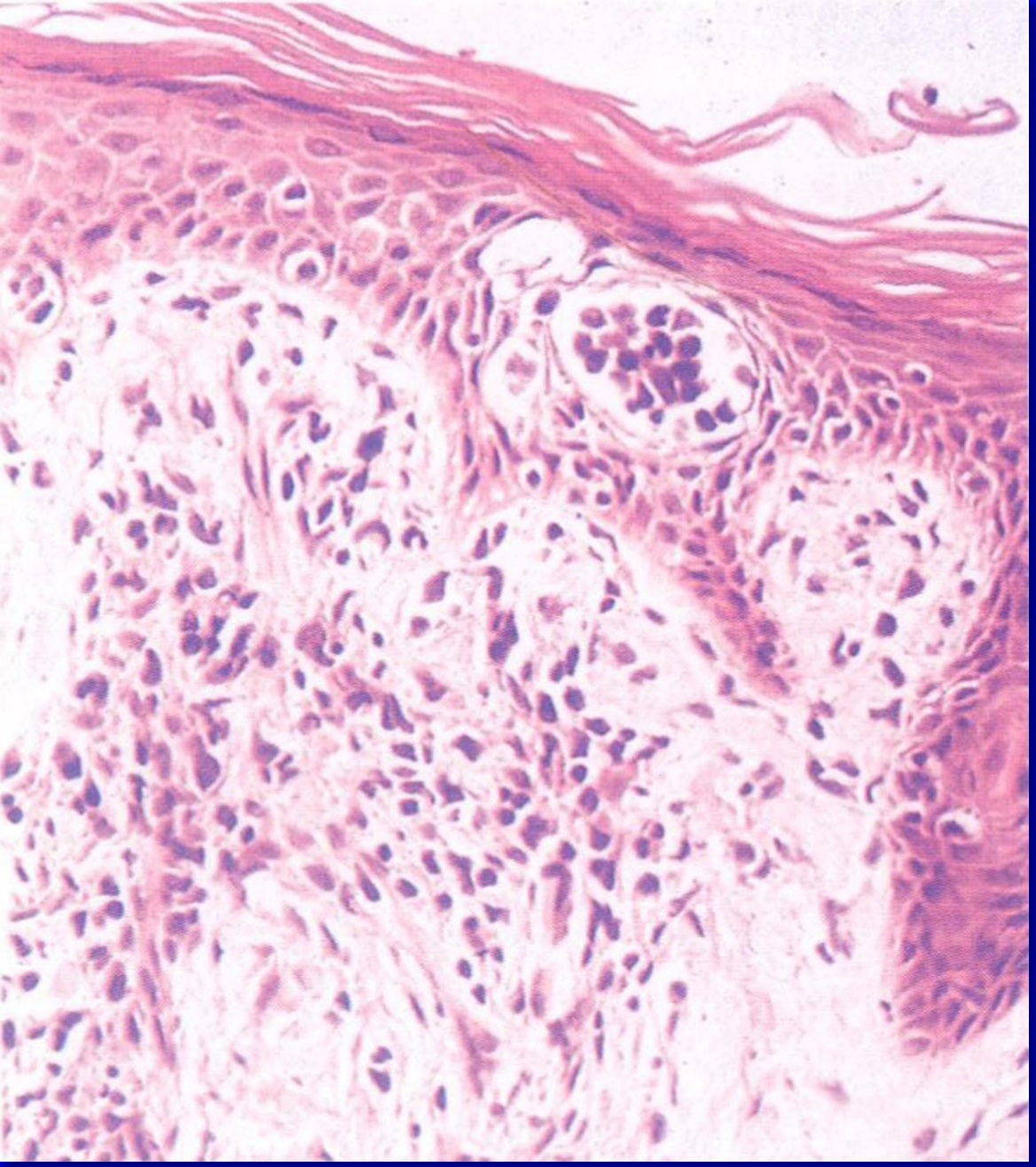

Mycosis fungoides.
Histological picture

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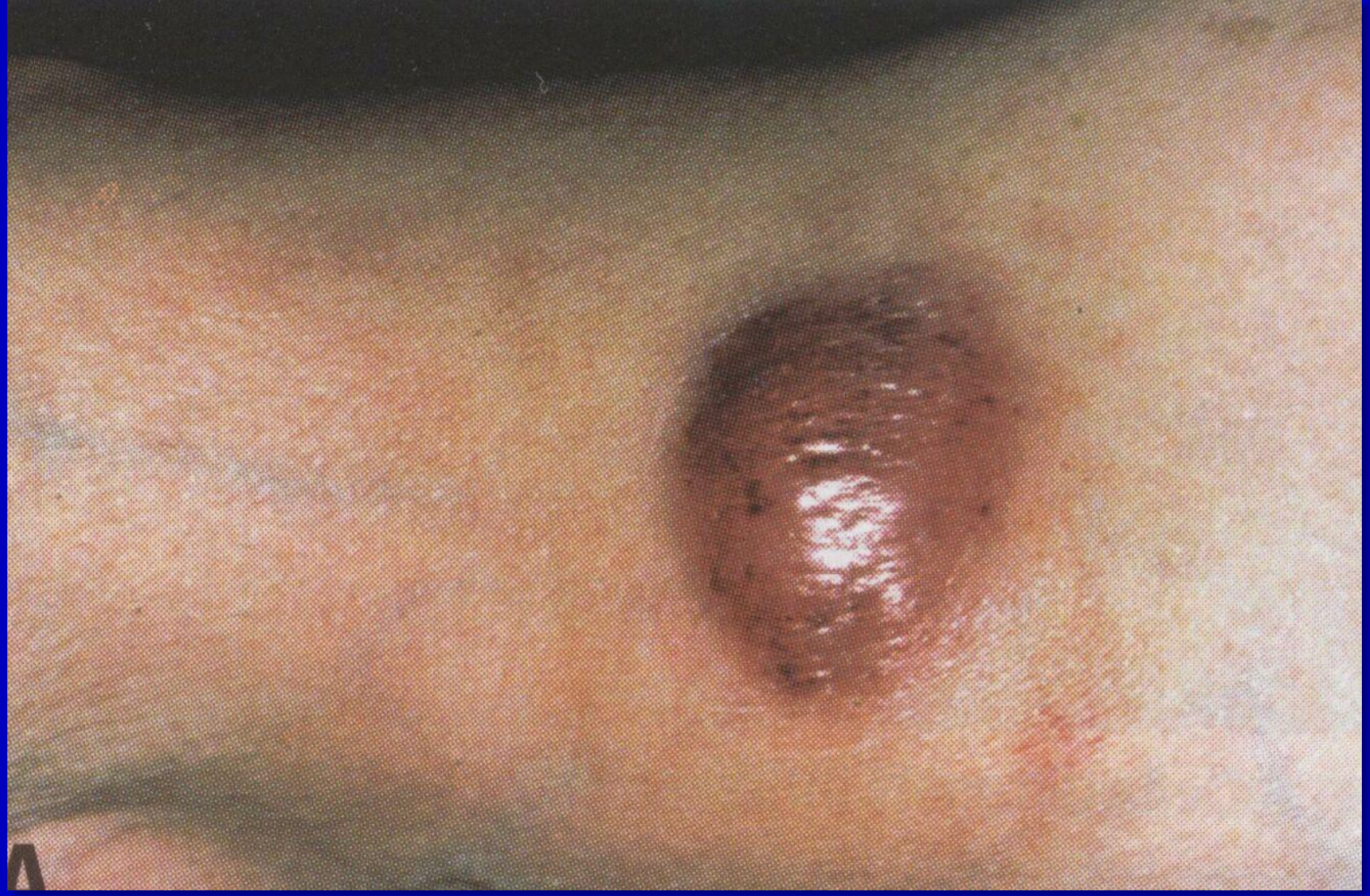

NHL. Skin specific infiltration.

Primary extranodal lymphomas

- If there are uncertain formations, infiltrative changes and suspicion of lymphoma, diagnosis can be confirmed only by tissue biopsy
  - Usually inflammation or malignancy is suspected
  - In cases of skin lymphomas, biopsy is often performed after prolonged clinical presentation

Conclusions

- NHL diagnosis is confirmed by histological conclusion
- In NHL case it is possible that there are no complaints, nor any laboratorial changes
- In cases of unclear skin changes tissue biopsy should be performed more often
- The use of therapeutic monoclonal antobodies in treatment has significantly improved the prognosis for B cell CD-20+ NHL

NHL forward Zemguz Girgensons – Bufalo Sabre