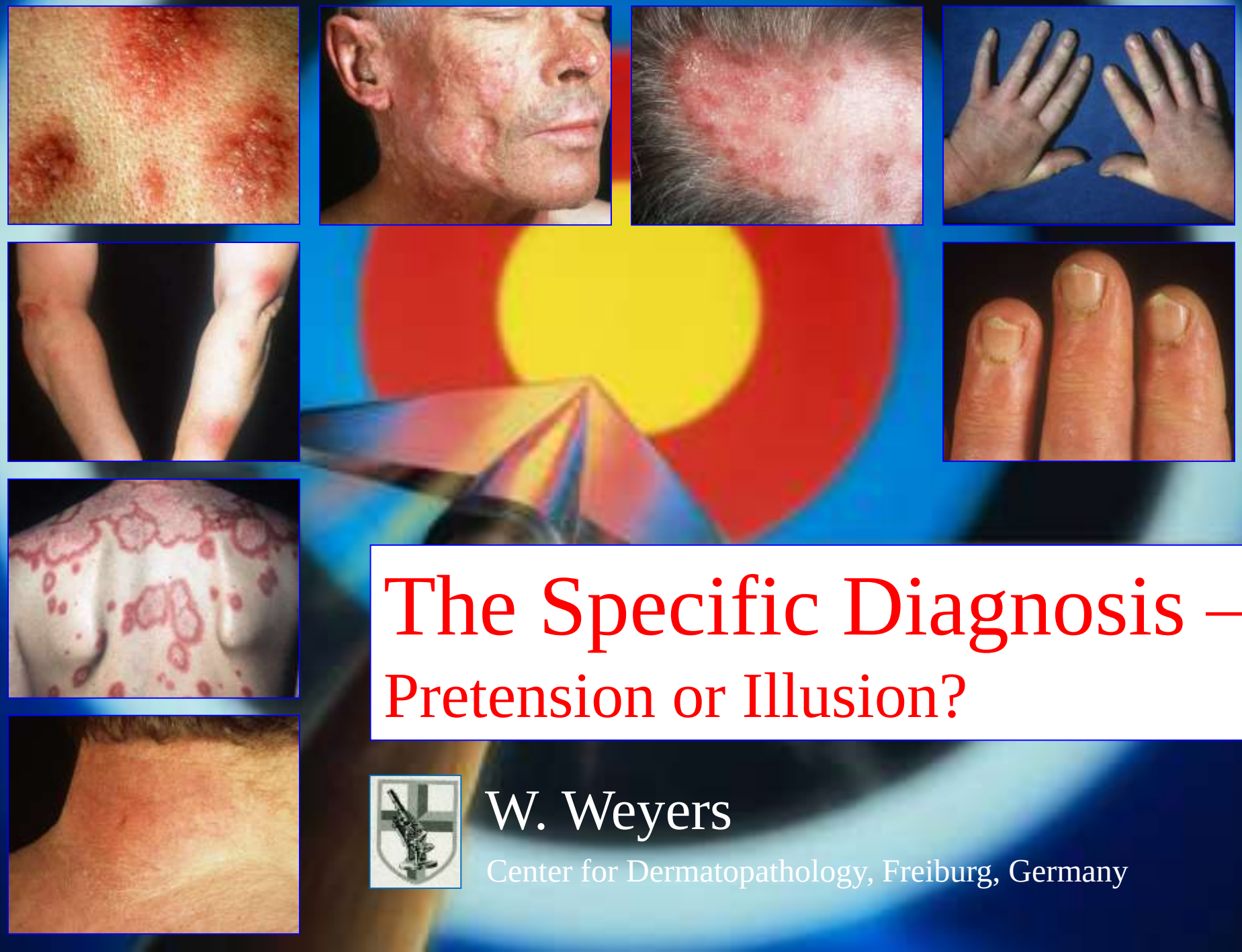


The Specific Diagnosis – Pretension or Illusion?

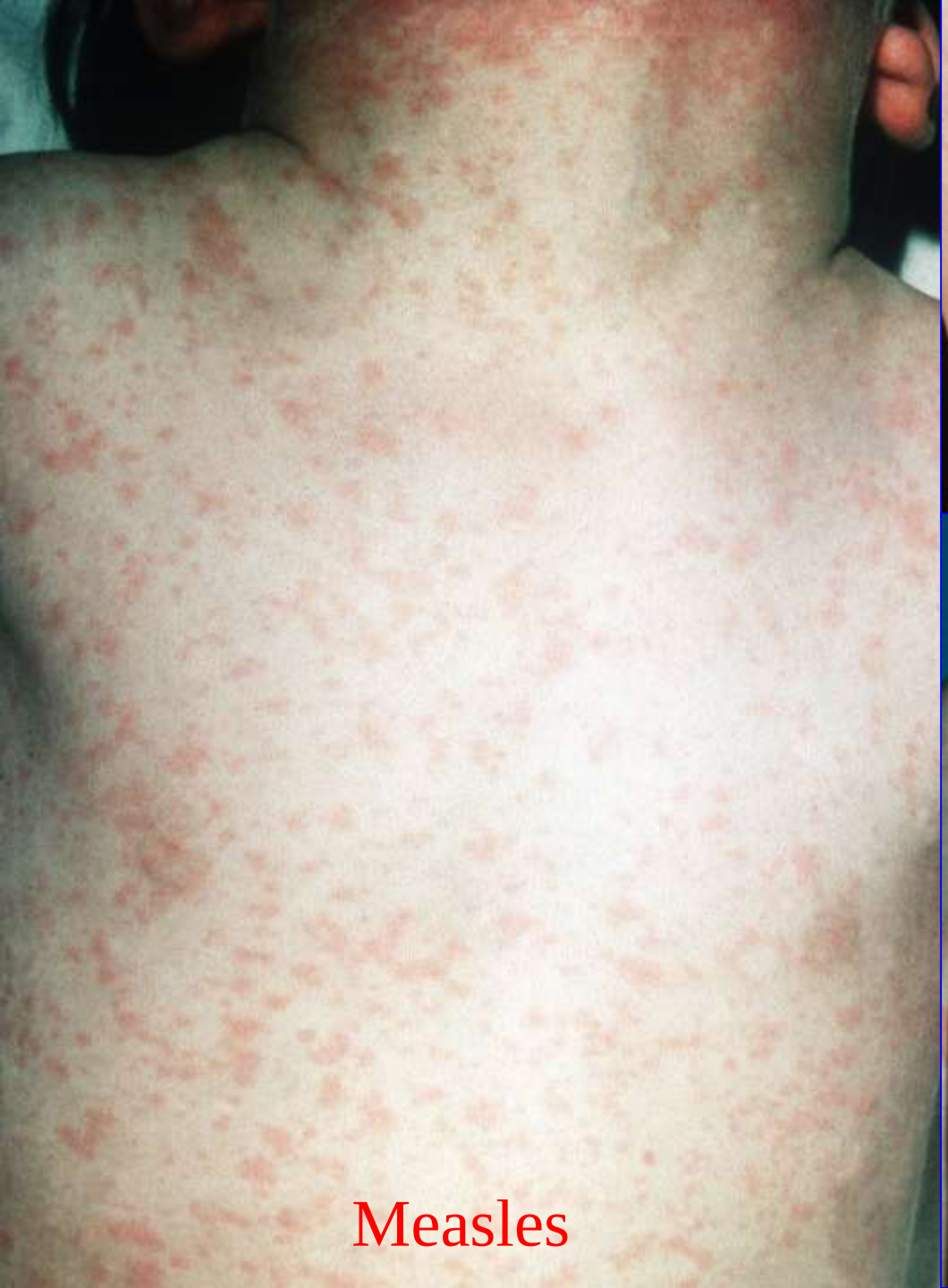
W. Weyers

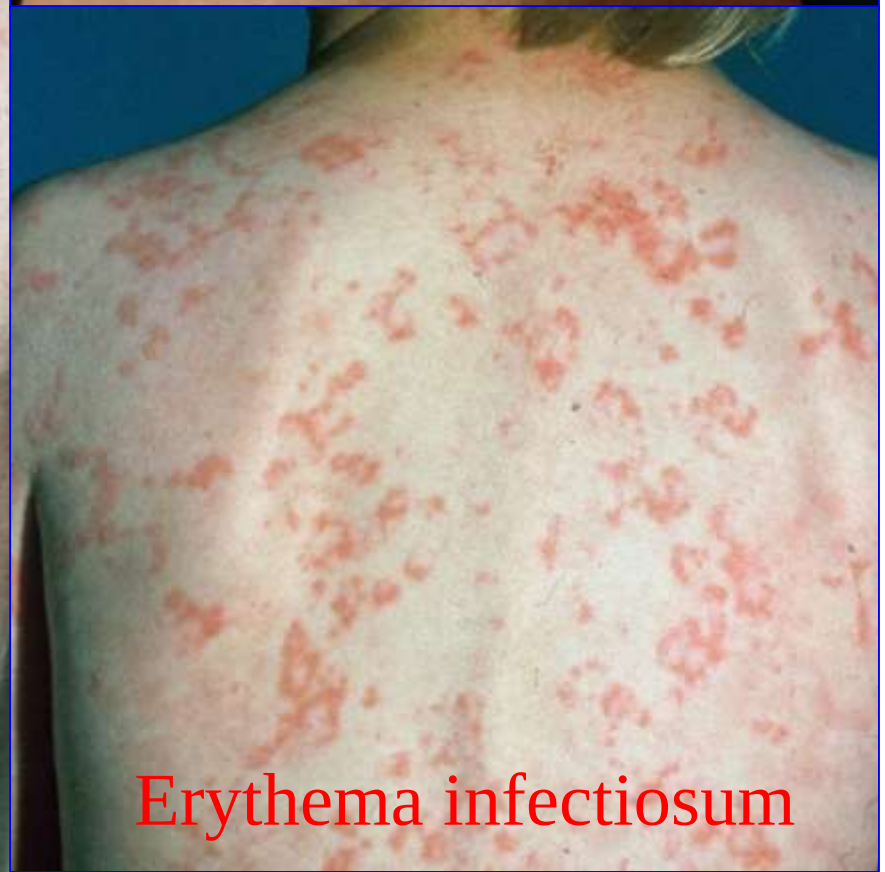
Center for Dermatopathology, Freiburg, Germany

The Specific Diagnosis – Pretension or Illusion ?

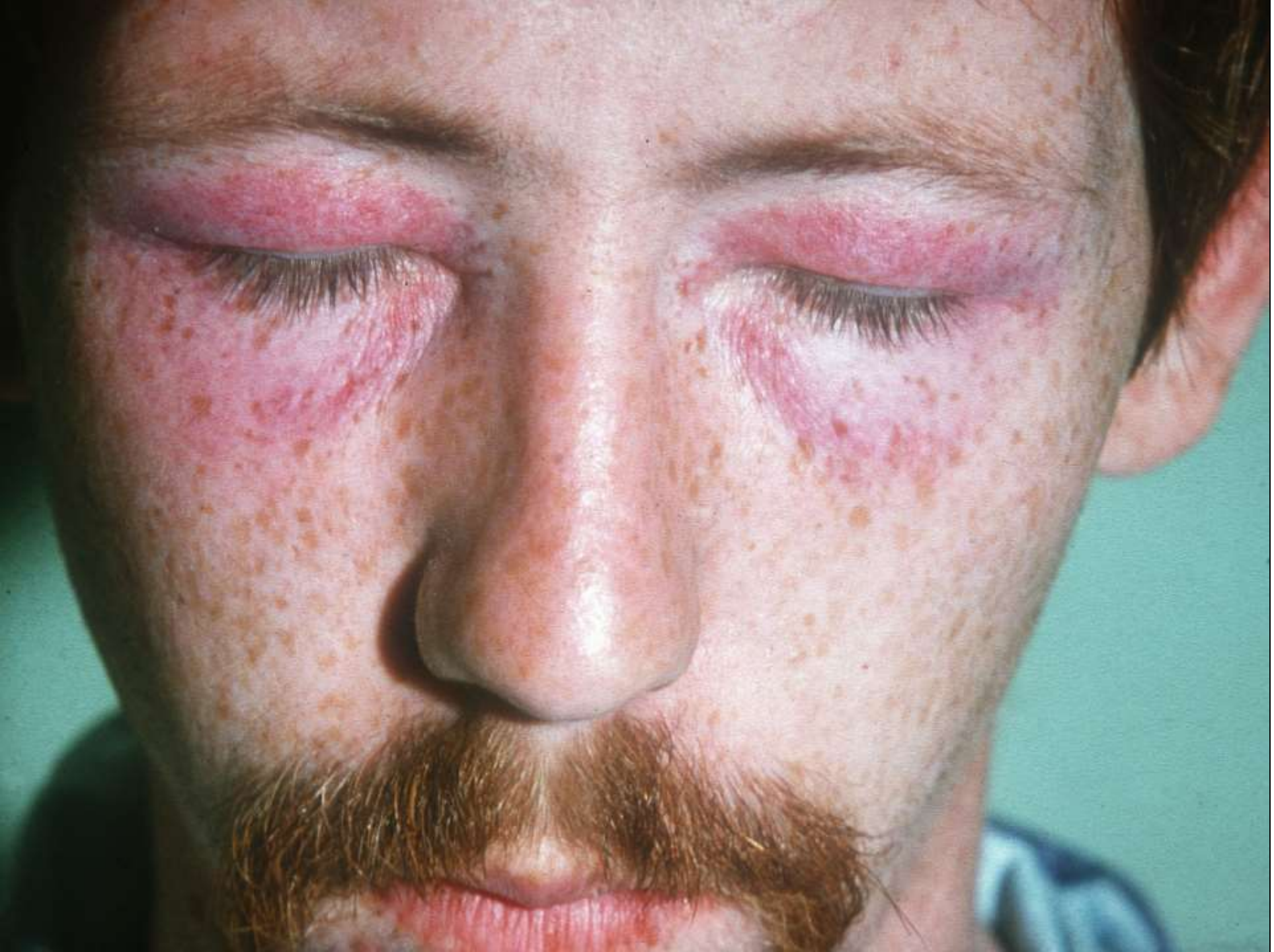
National Specialist Dermatopathology EQA meeting, Liverpool, May 22nd, 2020

The specific diagnosis stands in the center of medicine. It is the foundation of everything else: first the diagnosis, then the treatment. This is especially true for dermatology because skin lesions are among the most important clues for diagnosis. Many systemic diseases were first described on the basis of cutaneous lesions and continue to be recognized by them. This is surprising, fascinating, and not yet understood.

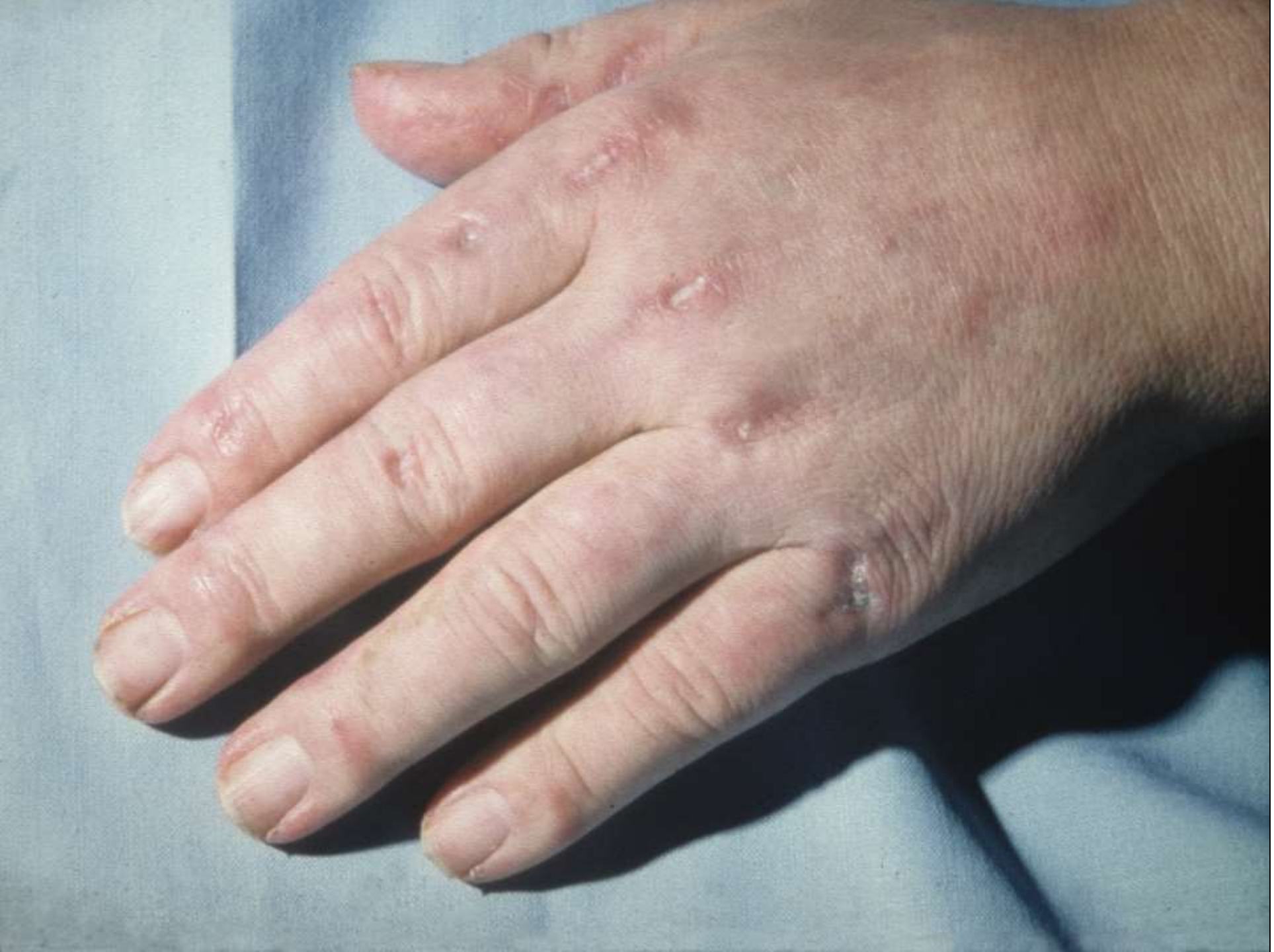




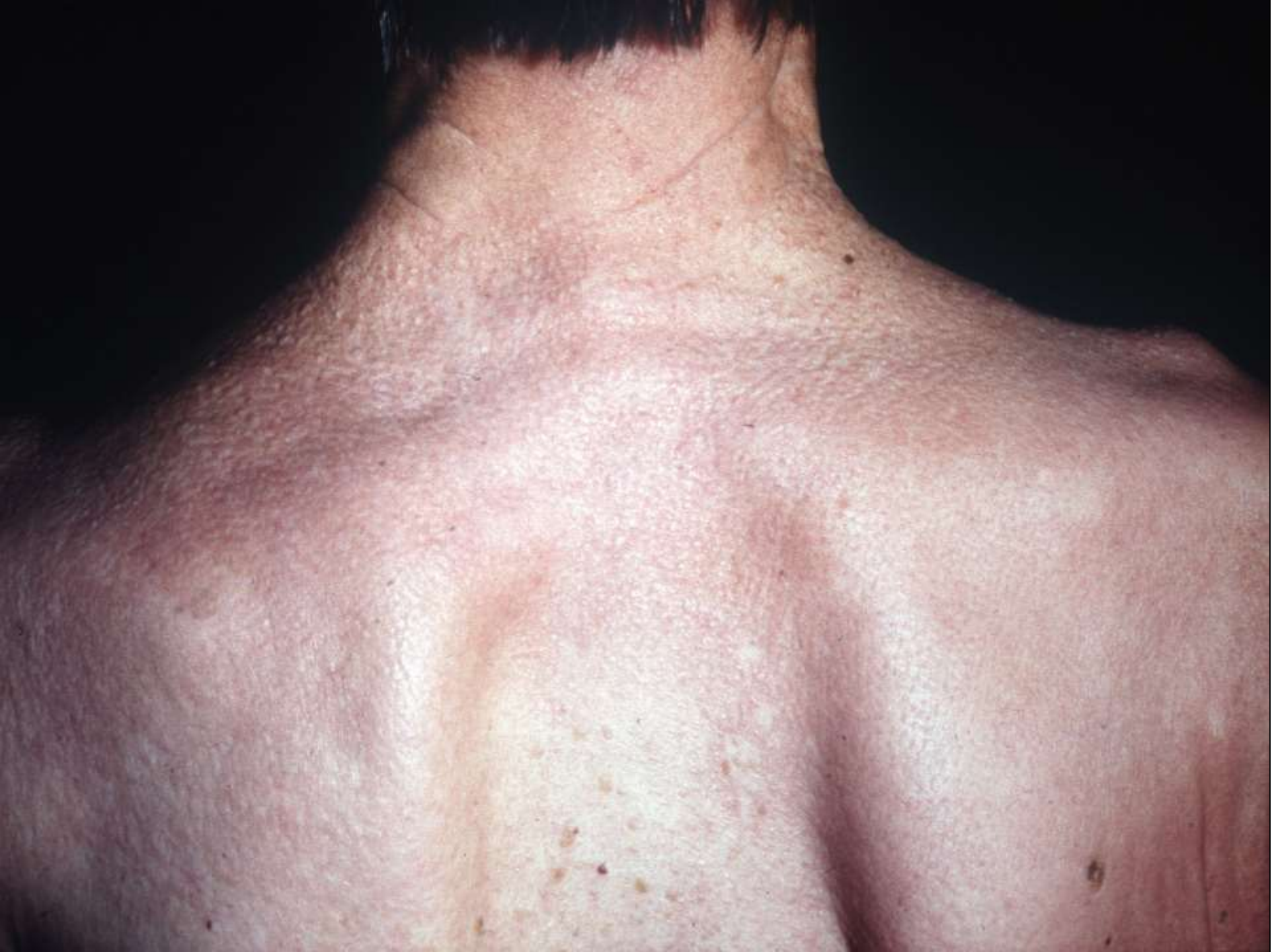
If an erythema results from dilatation of cutaneous blood vessels, why is it that the exanthema of measles differs from that of rubella and erythema infectiosum and that those differences allow for inferences concerning the responsible virus.



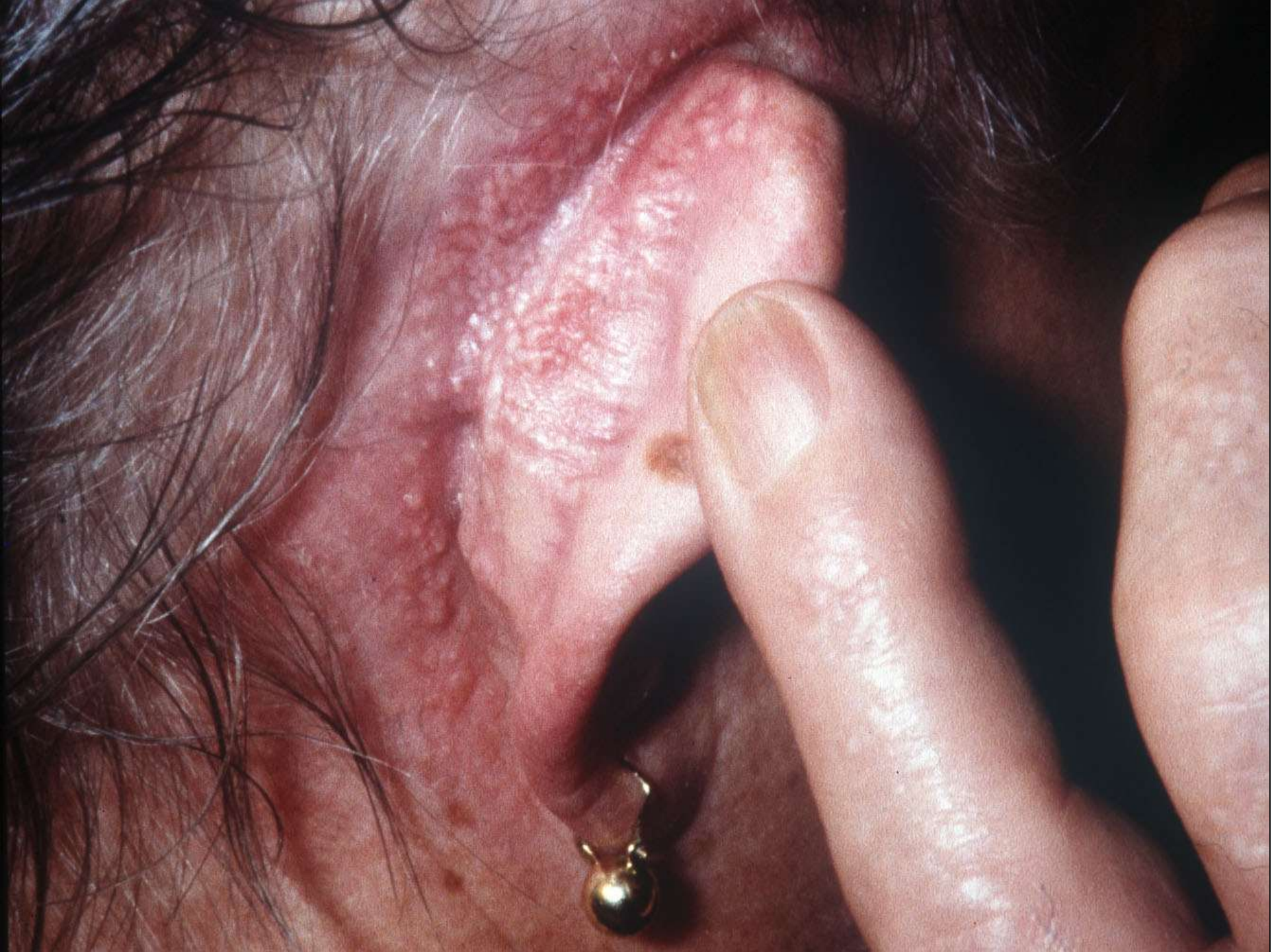
Why are a livid periocular edema



and centrally depressed papules above the interphalangeal joints associated with muscle pain and indicate that the patient suffers from dermatomyositis.

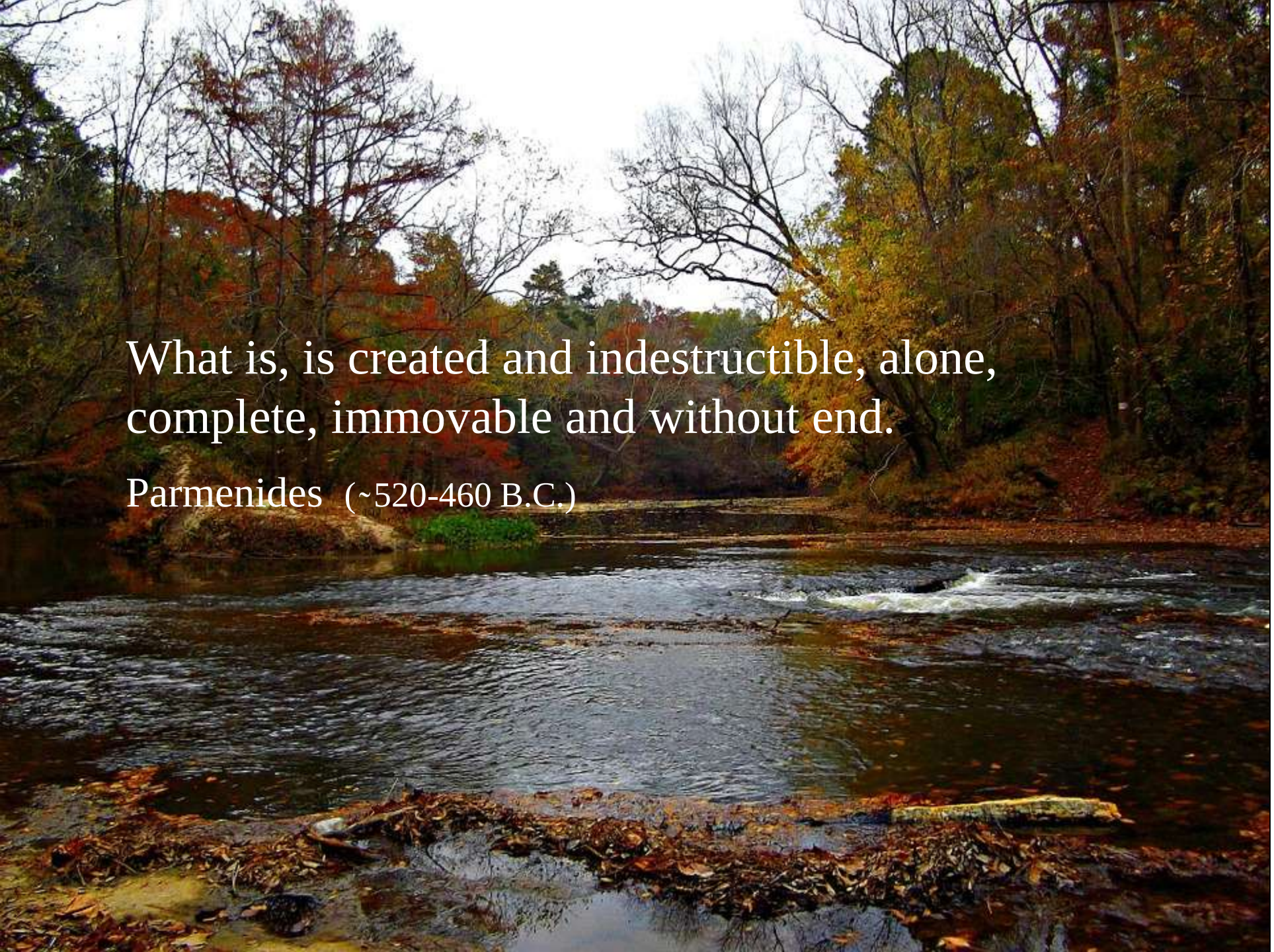


Why is massive thickening of the skin of the back a sign of monoclonal paraproteinemia and why can that suspicion be corroborated

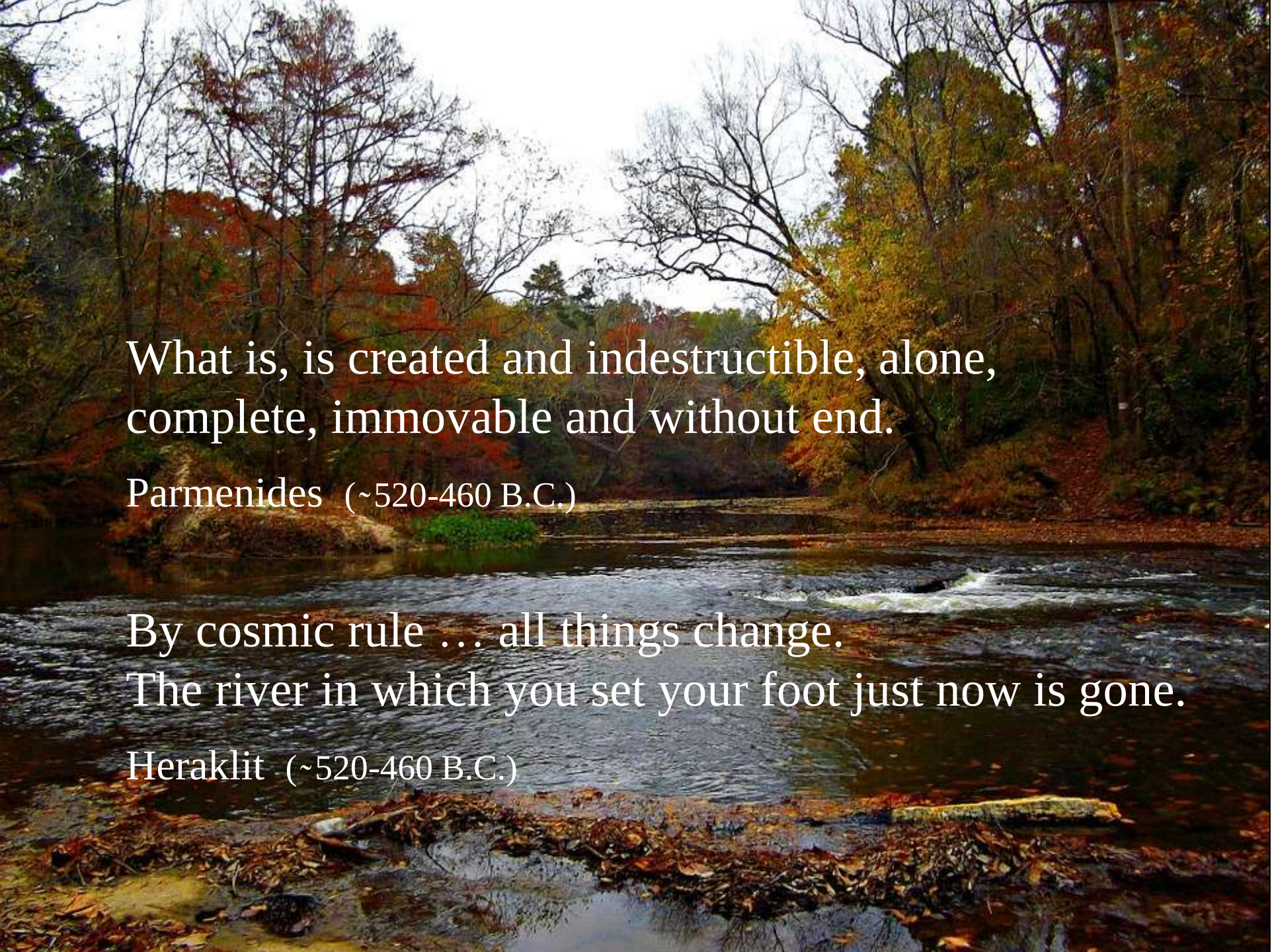


by a glance behind the ears where one sees tiny papules typical of scleromyxedema? It almost seems as if specific living entities had taken hold of the body in order to transform it according to their will. And yet, there are so many types of eruptions with so many cases deviating from the stereotypic presentation that the idea of any specificity is challenged.

The difficulty to come to grips with the constancy, and yet tremendous diversity, of nature does not only affect dermatology and medicine, but is a problem of biology at large. For millenia, naturalists and philophers have struggled with the problem of specificity, and the explanations given were often opposed diametrically.



For example, in the 4th century B.C., Greek philosopher Parmenides denied the possibility of any true change: *"What is, is created and indestructible, alone, complete, immovable and without end."* Hence, everything that existed was specific.

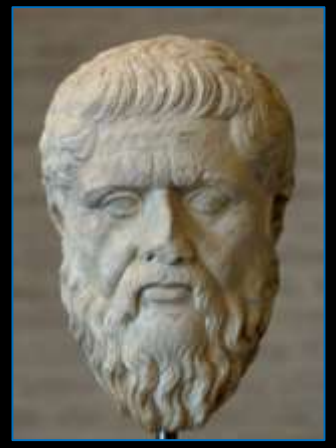


At the same time, a few hundred miles to the East, Heraclitus of Ephesos asserted just the opposite, namely that *“by cosmic rule … all things change”* and that *“the river where you set your foot just now is gone.”*According to his doctrine of “patha rhei,” “everything flows,” nothing was specific.

These elements … penetrating through each other … become one thing in one place and another in another … while ever they remain … the same.

Empodokles (~495-435 B.C.)

Empedocles of Agrigent harmonized those opposing viws by attributing the diversity of nature to alterations in the constellation of four basic elements, namely, water, earth, air, and fire: *“These elements … penetrating through each other … become one thing in one place and another in another, while ever they remain …. the same.”*



Plato
(~520-460 B.C.)

“eidē”

His contemporary Plato went a step further: he believed that not only the basic elements remained the same but also the ways they were arranged; in his view, their constellation was governed by eternal plans to which he referred as ideas or “eidē.” Those “eidē” were considered to be ontological realities and perfect models for a given entity,



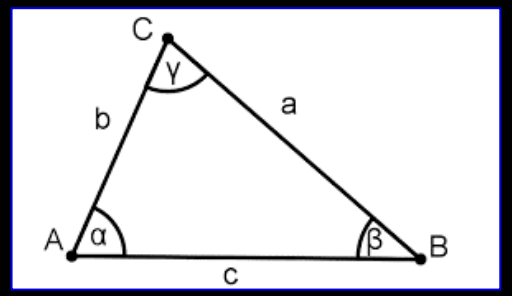


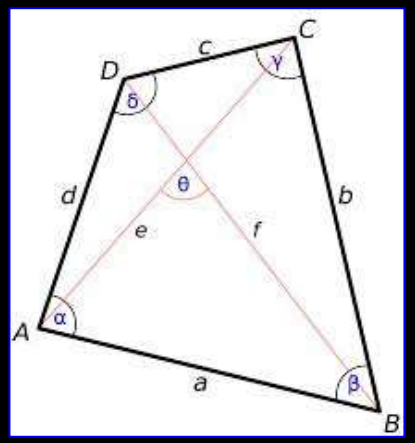



such as a horse. In Plato’s eyes, individual horses did not stand in any special relation to each other but were merely expressions of the same “eidos.” The most beautiful horse was the best expression of the “eidos,” variants being imperfect manifestations of it,

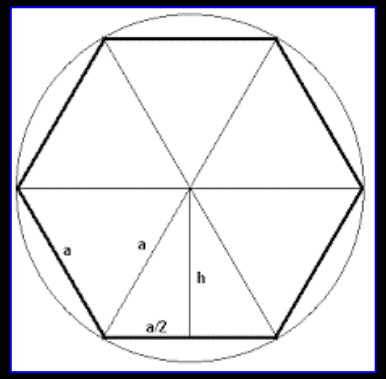
“eidos”

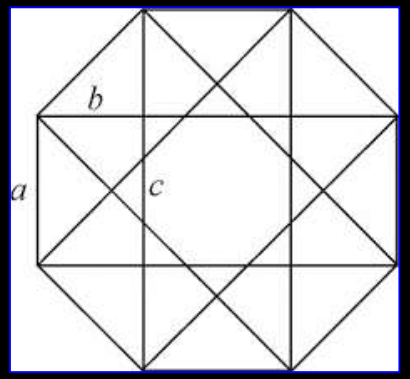
whereas other species were expressions of a different “eidos.”





“eidos”





The concept of species as discontinuous classes had its roots in geometry. The observation that a triangle, no matter what combination of angles it has, remains a triangle, discontinuously different from a quadrangle or any other polygon, became the basis of essentialism. Plato believed in the existence of eternal forms of reality that had been created once and for all. In order to uncover the eternal “logos,” he proposed a method of classification by binary division of contraries until the object being classified was reached, e.g., water vs. land animals, and herbivors vs. carnivors.

However, because he regarded living objects as imperfect representations of an eternal plan, he showed little interest in any aspect of the terrestrial world, and because his concept of eternal ideas and neglect for the material world fitted well with Christian dogma, natural history studies were discredited for centuries.

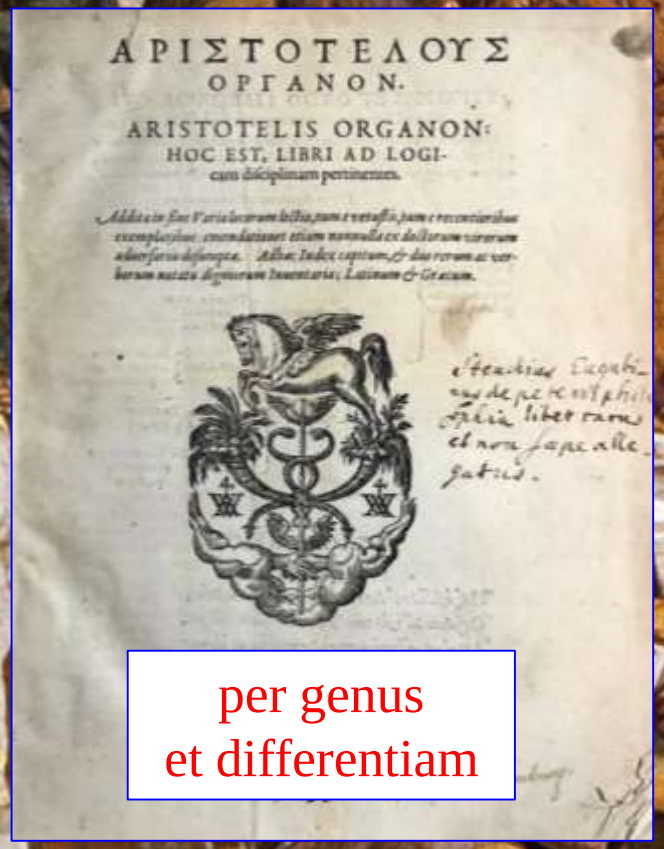
ΑΡΙΣΤΟΤΕΛΟΥΣ
ΟΡΓΑΝΟΝ.

ARISTOTELIS ORGANON:
HOC EST, LIBRI AD LOGI-
cam disciplinam pertinentes.

FRANCOFVRDI
Apud heredes Andreæ Wecheli,
MDLXXXV.

By contrast, Plato's onetime pupil Aristotle wrote several books of a biological nature and proposed a method of classification that came to be known

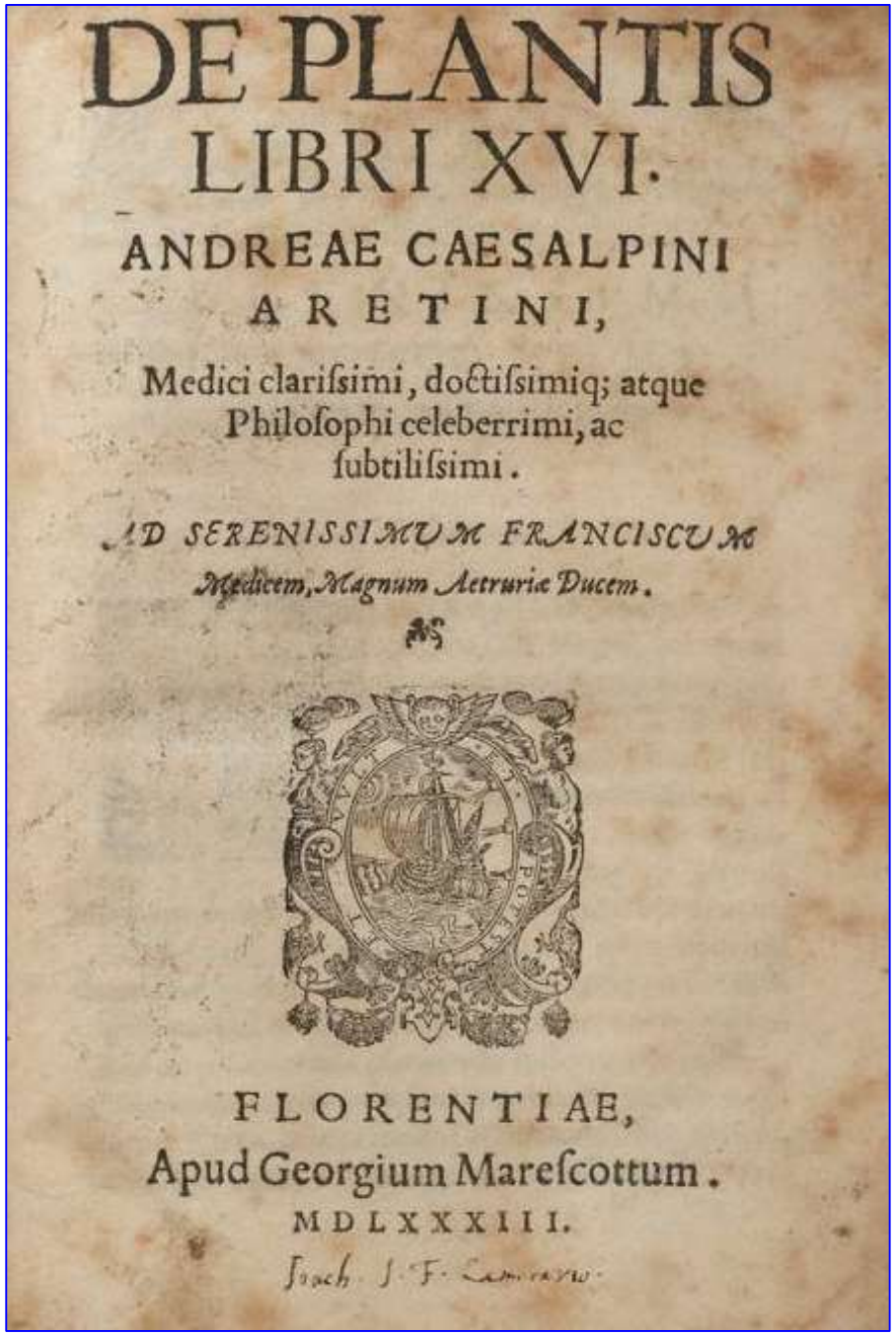
Plato Aristotle

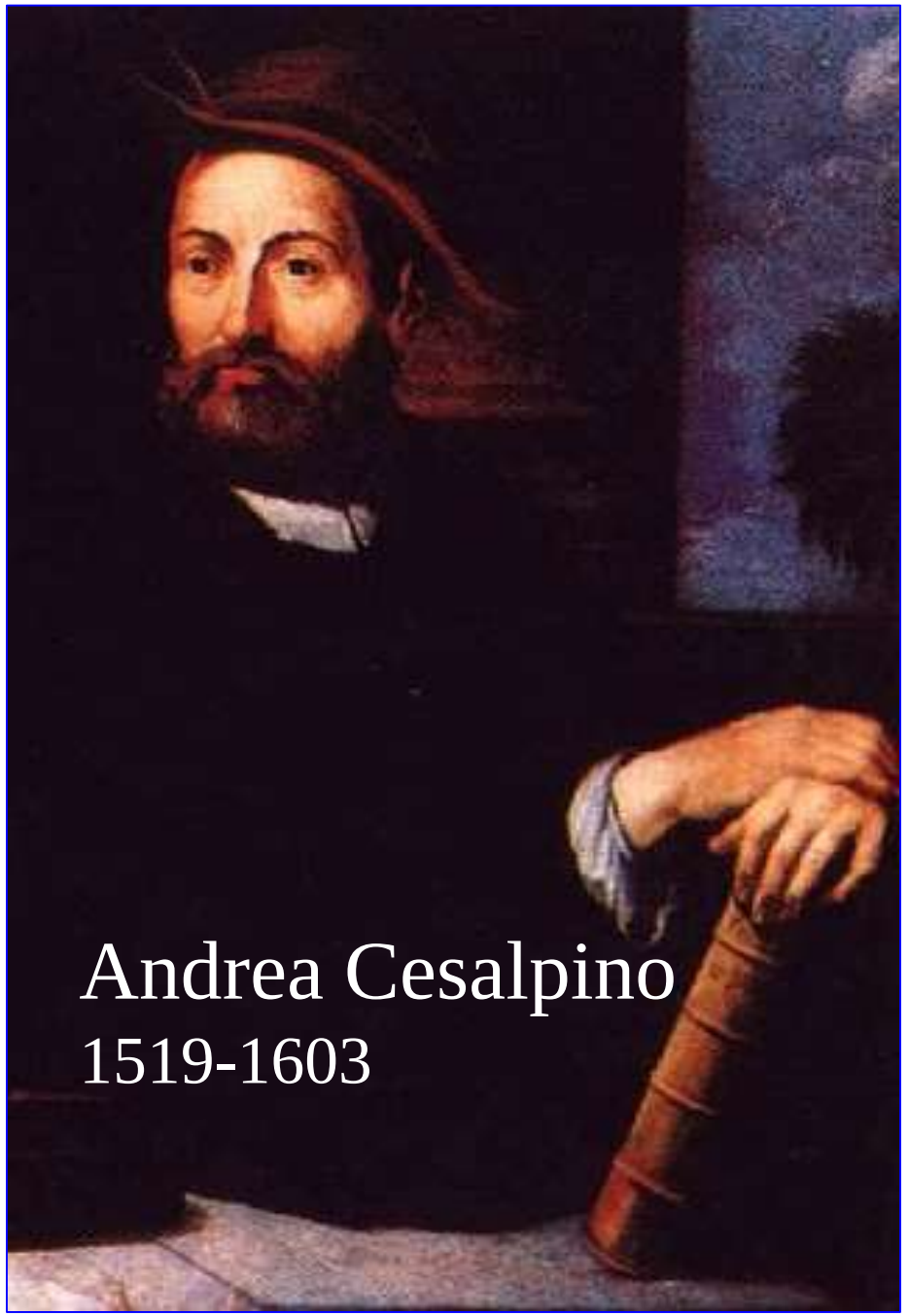

ΑΡΙΣΤΟΤΕΛΟΥΣ
ΟΡΓΑΝΟΝ.

ARISTOTELIS ORGANON:
HOC EST, LIBRI AD LOGI-
cam disciplinam pertinentes.

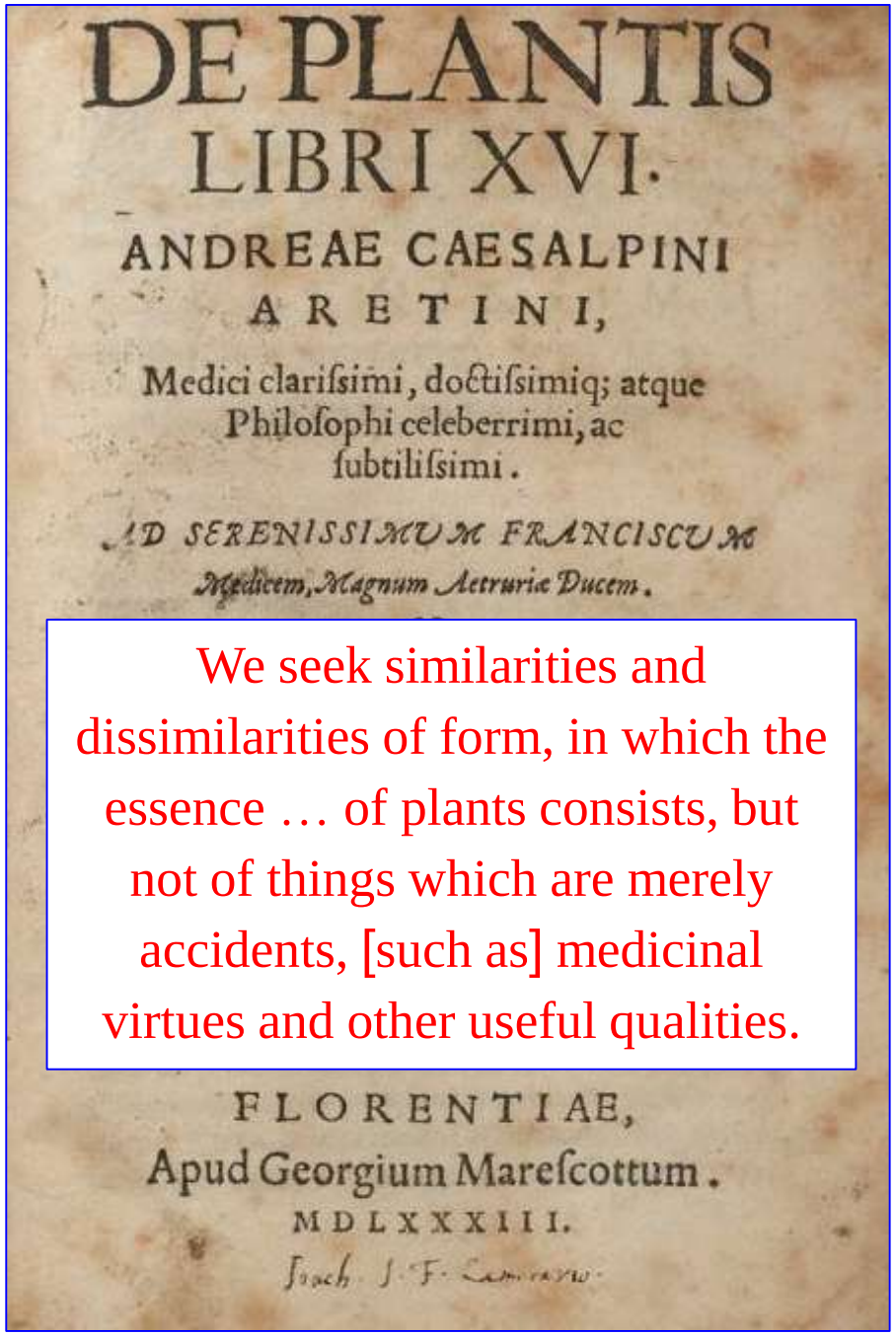
per genus
et differentiam

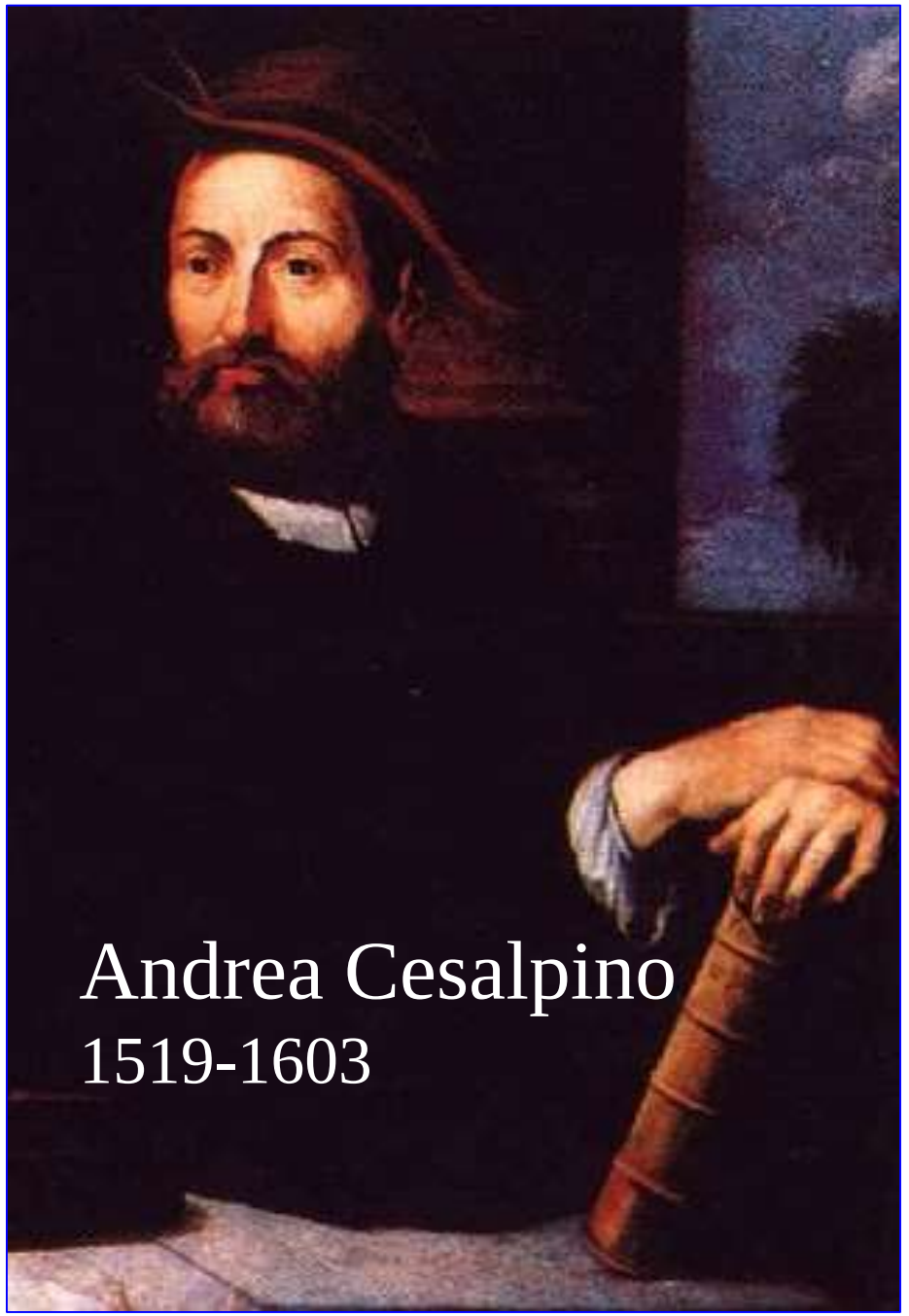
as “per genus et differentiam,” i.e., genera were defined on the basis of common attributes, and species were distinguished by differences among members of the same genus. Aristotle also alluded to “accidents” (symbebekos) that led to minor modifications without being an essential element of species.
When his writings were rediscovered at the beginning of the Renaissance, natural history studies were resumed in the Aristotelian tradition.


DE PLANTIS
LIBRI XVI.
ANDREAE CAESALPINI
ARETINI,
Medici clariſsimi, doctiſsimiq; atque
Philoſophi celeberrimi, ac
ſubtiliſsimi.
AD SERENISSIMUM FRANCISCUM
Medicem, Magnum Aetruriæ Ducem.
FLORENTIAE,
Apud Georgium Mareſcottum.
MDLXXXIII.

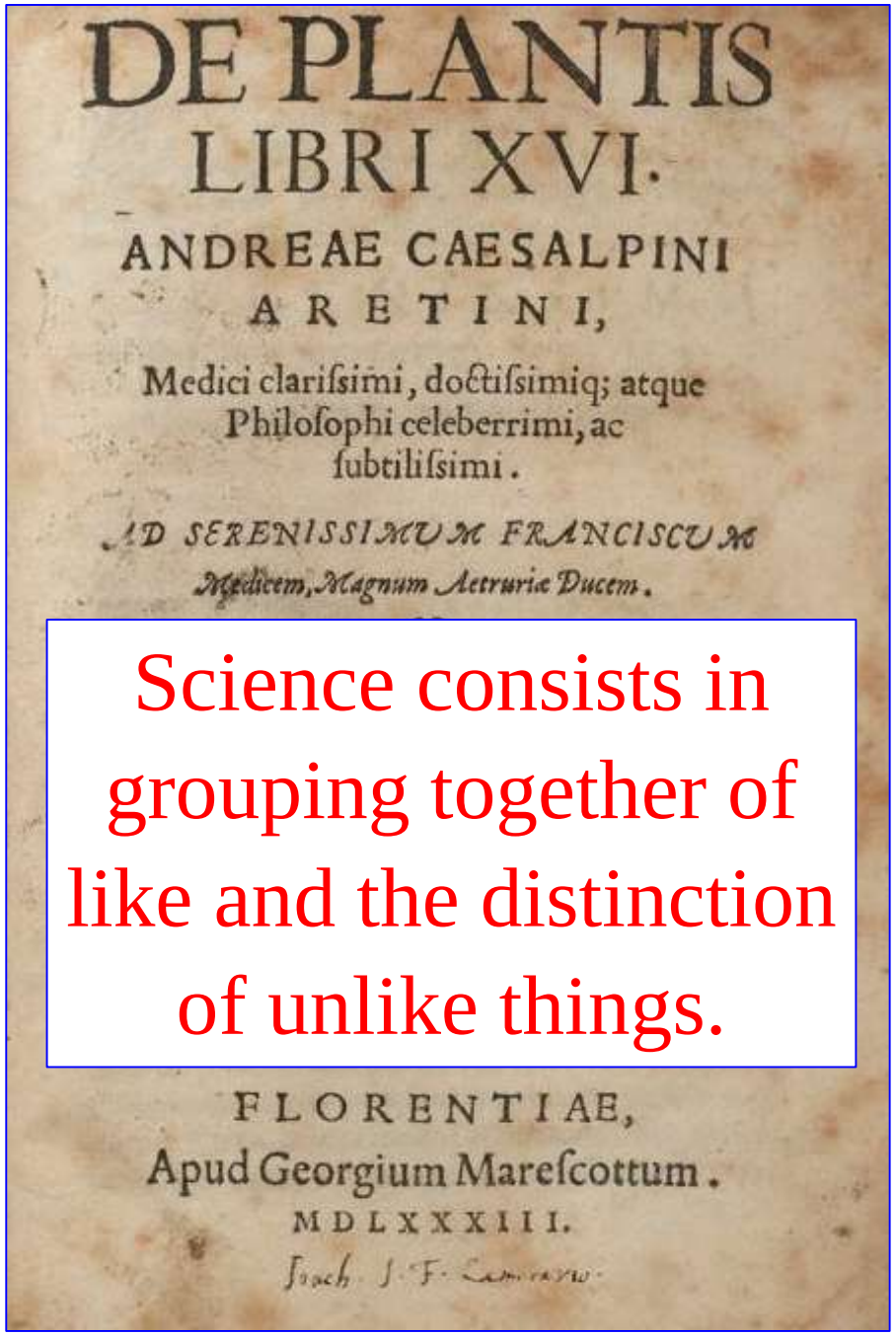


For example, in his book “De plantis,” published in Florence in 1593, Andrea Cesalpino explained


DE PLANTIS
LIBRI XVI.
ANDREAE CAESALPINI
ARETINI,
Medici clariſsimi, doctiſsimiq; atque
Philoſophi celeberrimi, ac
ſubtiliſsimi.
AD SERENISSIMUM FRANCISCUM
Medicem, Magnum Aetruriæ Ducem.
We seek similarities and dissimilarities of form, in which the essence … of plants consists, but not of things which are merely accidents, [such as] medicinal virtues and other useful qualities.
FLORENTIAE,
Apud Georgium Mareſcottum.
MDLXXXIII.


Andrea Cesalpino
1519-1603

that *“we seek similarities and dissimilarities of form, in which the essence … of plants consists, but not of things which are merely accidents,”* such as *“medicinal virtues and other useful qualities.”*


DE PLANTIS
LIBRI XVI.
ANDREAE CAESALPINI
ARETINI,
Medici clariſsimi, doctiſsimiq; atque
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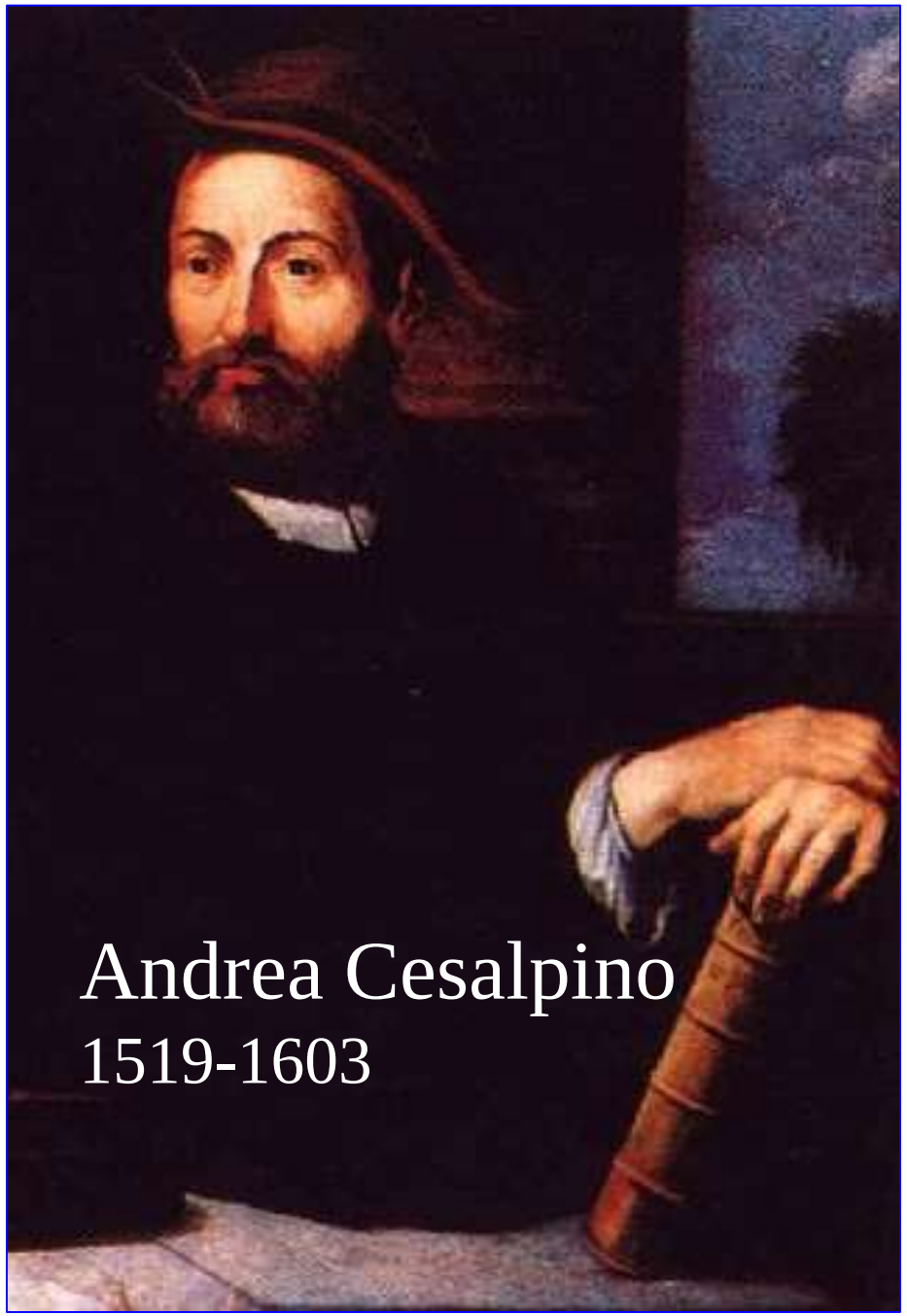
ſubtiliſsimi.
AD SERENISSIMUM FRANCISCUM
Medicem, Magnum Aetruriæ Ducem.
FLORENTIAE,
Apud Georgium Mareſcottum.
MDLXXXIII.

Science consists in grouping together of like and the distinction of unlike things.


Andrea Cesalpino
1519-1603

In the preface, Cesalpino pointed out that *"science consists in grouping together of like and the distinction of unlike things."*

In nature, however, similar species can be completely unrelated, such as insects mimicking sticks or leafs,

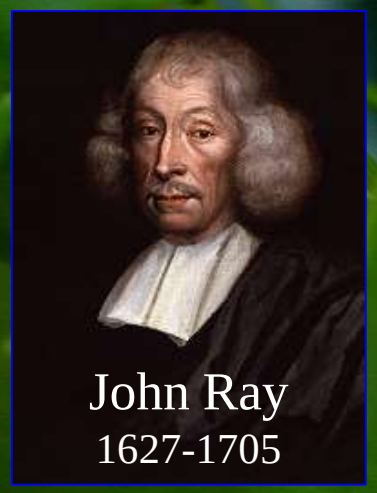
whereas strikingly different organisms may belong to the same species, such as caterpillars and butterflies. Hence, biological classifications cannot rely on similarities and differences but must also take into account other factors.

A. Cesalpino
1519-1603

According to the law of nature like always produces like.

Andrea Cesalpino, 1593

This was already acknowledged by Cesalpino who noted *"that according to the law of nature like always produces like,"* thus foreshadowing



John Ray
1627-1705

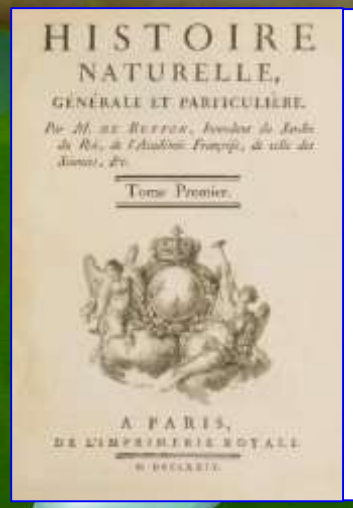
No surer criterion for determining species has occurred to me than the distinguishing features that perpetuate themselves in propagation from seed. … one species never springs from the seed of another nor vice versa.

John Ray, 1686

the first biological definition of species that was given in 1686 by John Ray of London in these words: *"No surer criterion for determining species has occurred to me than the distinguishing features that perpetuate themselves in propagation from seed. … One species never springs from the seed of another nor vice versa."*

From there, it was only a small step

Georges-Louis Leclerc de Buffon
1707-1788



A species is a constant succession of similar individuals that can reproduce together.

Georges-Louis Leclerc de Buffon, 1749

to Buffon's definition of species, in his famous "Histoire naturelle" in 1749, as *"a constant succession of similar individuals that can reproduce together"* –

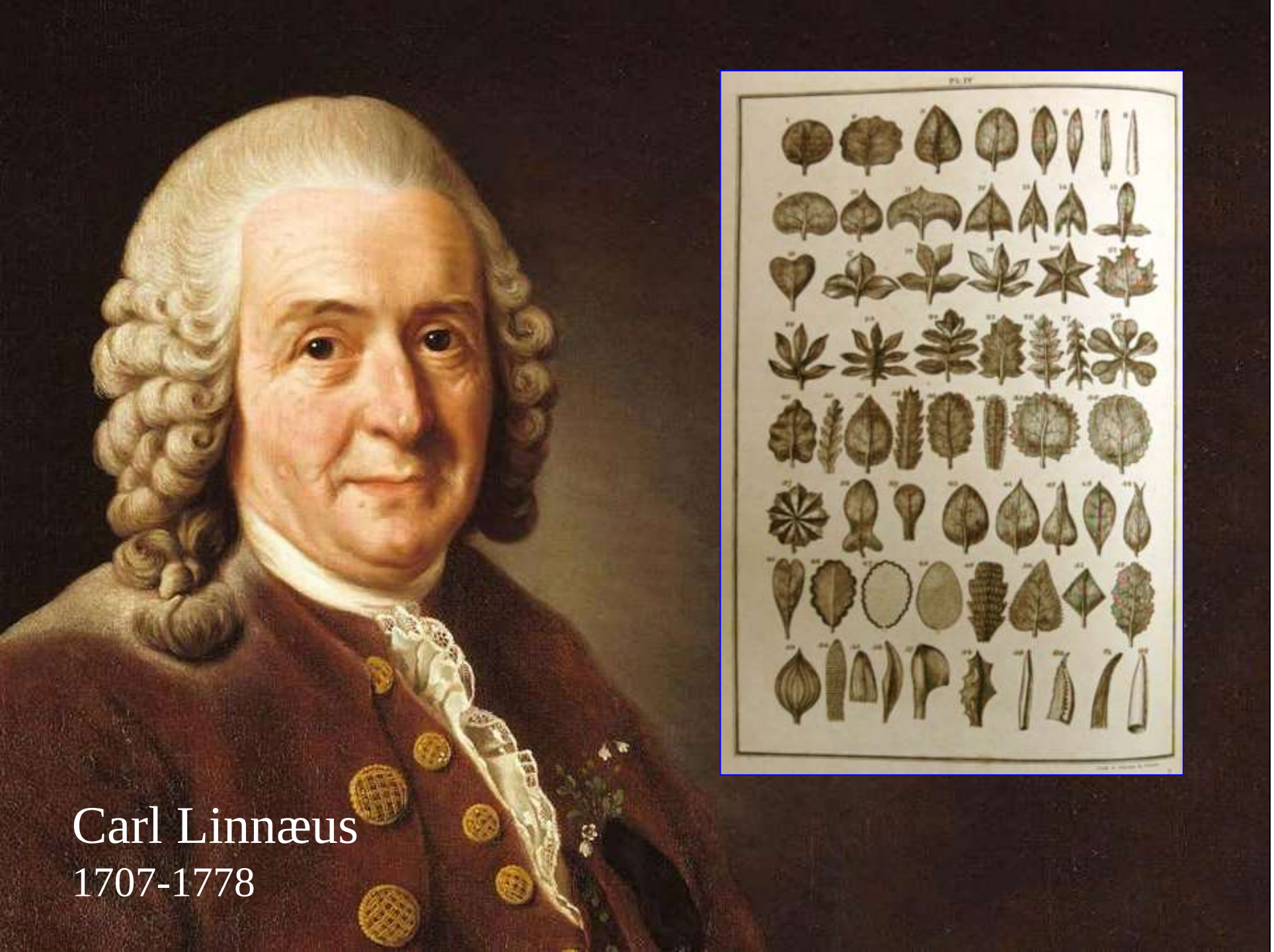

HISTOIRE
NATURELLE,
GÉNÉRALE ET PARTICULIÈRE.
Tome Premier.
A PARIS,

une production continue, perpétuelle, invariable.

Georges-Louis Leclerc de Buffon, 1749

“une production continue, perpétuelle, invariable.”

The problem that remained unresolved was distinction between different species and varieties of the same species. For centuries, the belief that all species had been created by God and were unchangeable, was set in stone



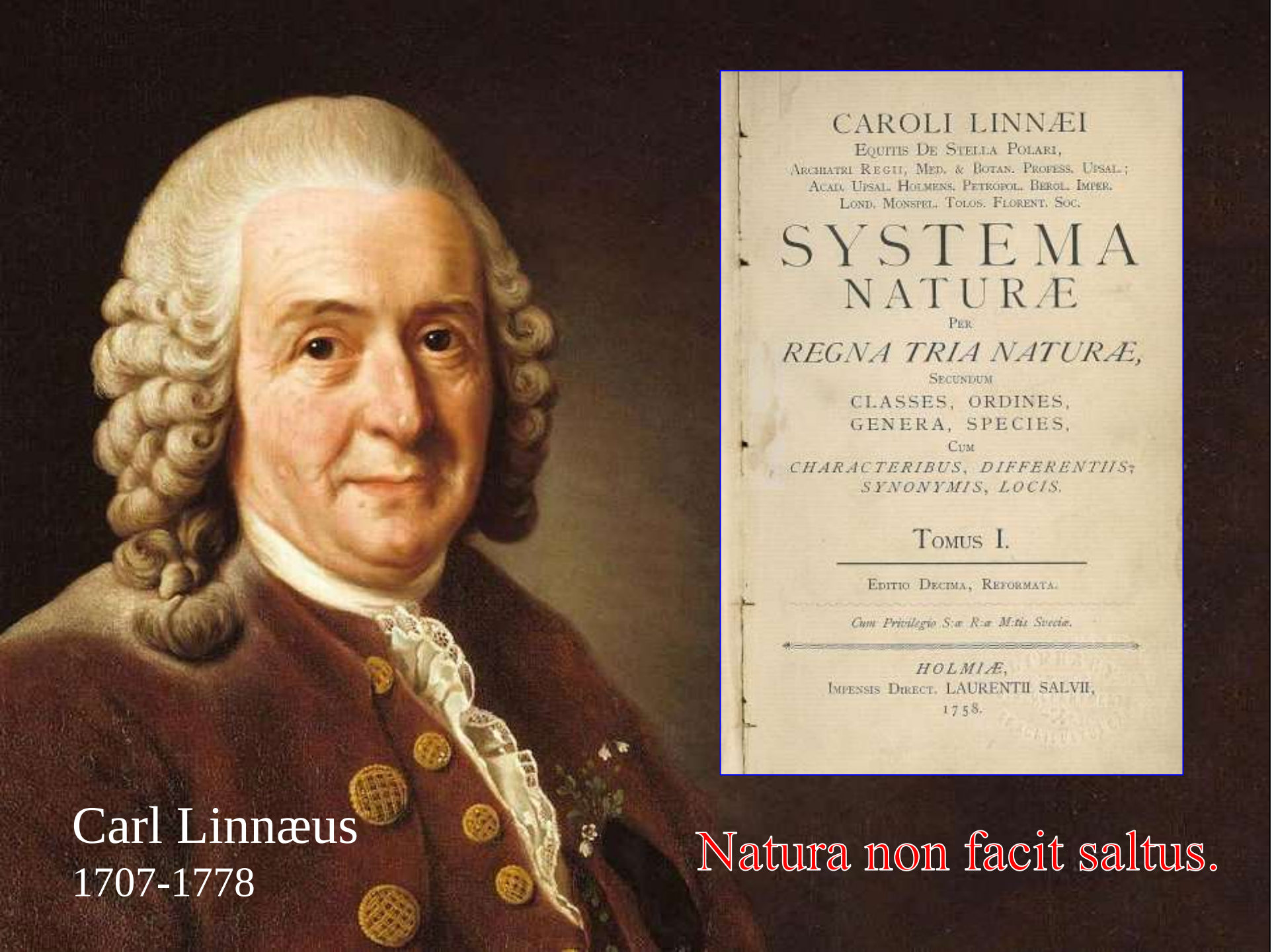
Carl Linnæus
1707-1778

was set in stone and was upheld by leading naturalists, such as Carl Linnæus of Sweden who coined the famous proverb,

Carl Linnæus
1707-1778

Natura non facit saltus.

“Nature makes no jumps,”
“Natura non facit saltus.”



Carl Linnæus
1707-1778

CAROLI LINNÆI
EQUITIS DE STELLA POLARI,
ARCHIATRI REGII, MED. & BOTAN. PROFESS. UPSAL.;
ACAD. UPSAL. HOLMENS. PETROPOL. BEROL. IMPER.
LOND. MONSPEL. TOLOS. FLORENT. SOC.

SYSTEMA NATURÆ

PER

REGNA TRIA NATURÆ,

SECUNDUM

CLASSES, ORDINES,
GENERA, SPECIES,

CUM

CHARACTERIBUS, DIFFERENTIIS,
SYNONYMIS, LOCIS.

TOMUS I.

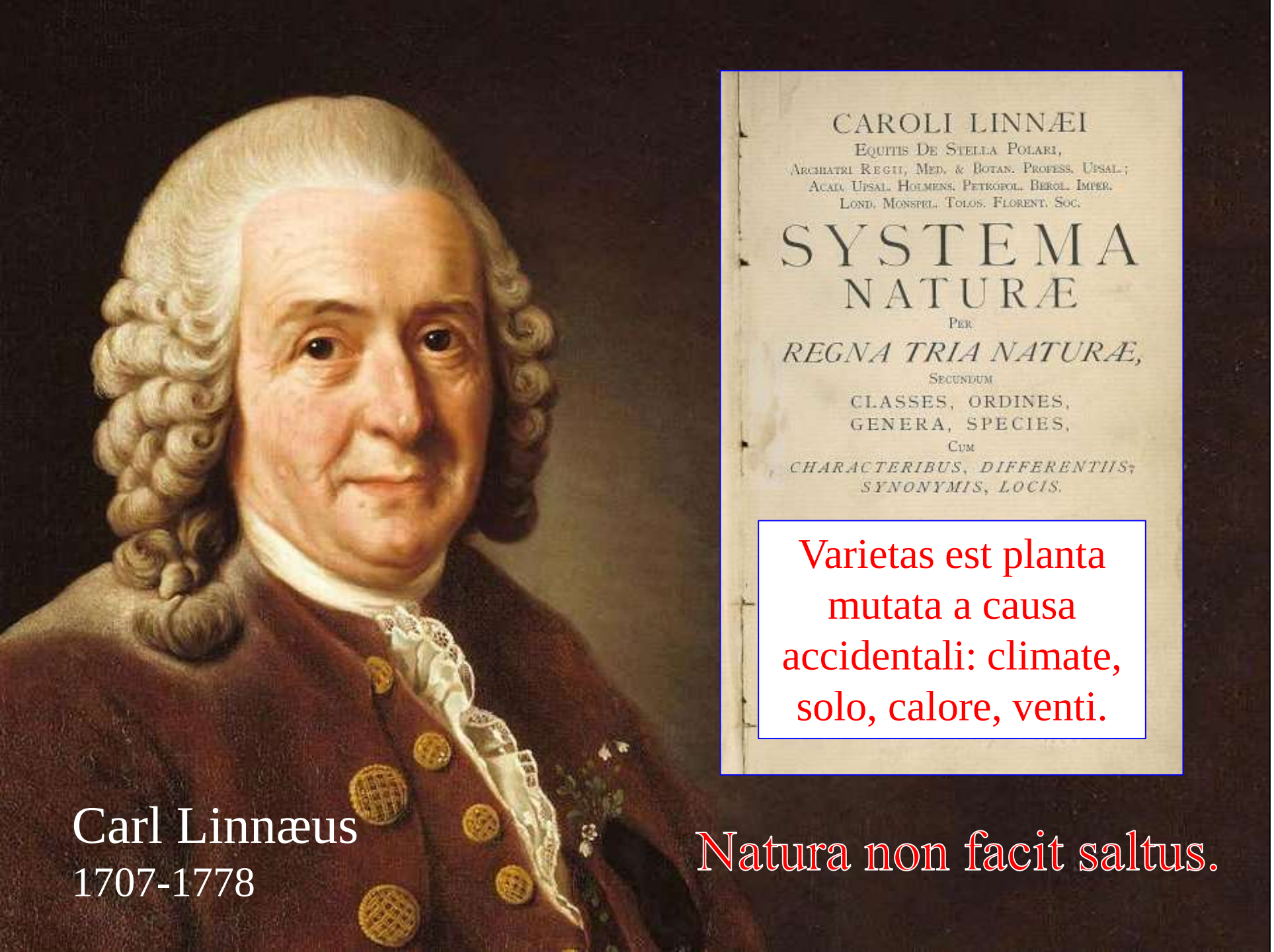
EDITIO DECIMA, REFORMATA.

Cum Privilegio S:æ R:æ M:tis Sveciæ.

HOLMIÆ,
IMPENSIS DIRECT. LAURENTII SALVII,
1758.

Natura non facit saltus.

In his famous “Systema naturae,” Linnæus distinguished classes, orders, genera, and species of plants on the basis of the number and arrangement of their stamens and pistils, and attributed varieties to external conditions alone:



Carl Linnæus
1707-1778

Natura non facit saltus.

"Varietas est planta mutata a causa accidentali: climate, solo, calore, venti." In other words, Linnæus believed that varieties were caused by influences such as climate, soil, heat, and wind, rather than genetic changes, and it took him decades to acknowledge that species were not unchangeable but could also result from hybridization.

Carl Linnæus
1707-1778

Natura non facit saltus.

Linnæus' "Systema naturae" proved to be very useful for the identification of plants. All a student of botany had to do for that purpose was to learn a limited number of names of the parts of the flower and fruit. Nonetheless, his method of classification, reducing a complex organism to a few attributes considered by him to represent its essence, was highly artificial and was criticized as such,

We must make use of all parts of the object which we have under consideration.

Georges-Louis Leclerc de Buffon, 1749

e.g., by Buffon who noted, in his *"Histoire naturelle,"* that we *"must make use of all parts of the object which we have under consideration."*

While some biologists struggled with the definition of species, others denied the legitimacy of that concept altogether. In his early years, Buffon himself alluded to the arbitrariness of biological classifications

Nature, proceding by unknown gradations, cannot wholly lend herself to divisions. … In general, the more one increases the number of one's divisions, in the case of products of nature, the closer one comes to the truth, since in reality individuals alone exist in nature.

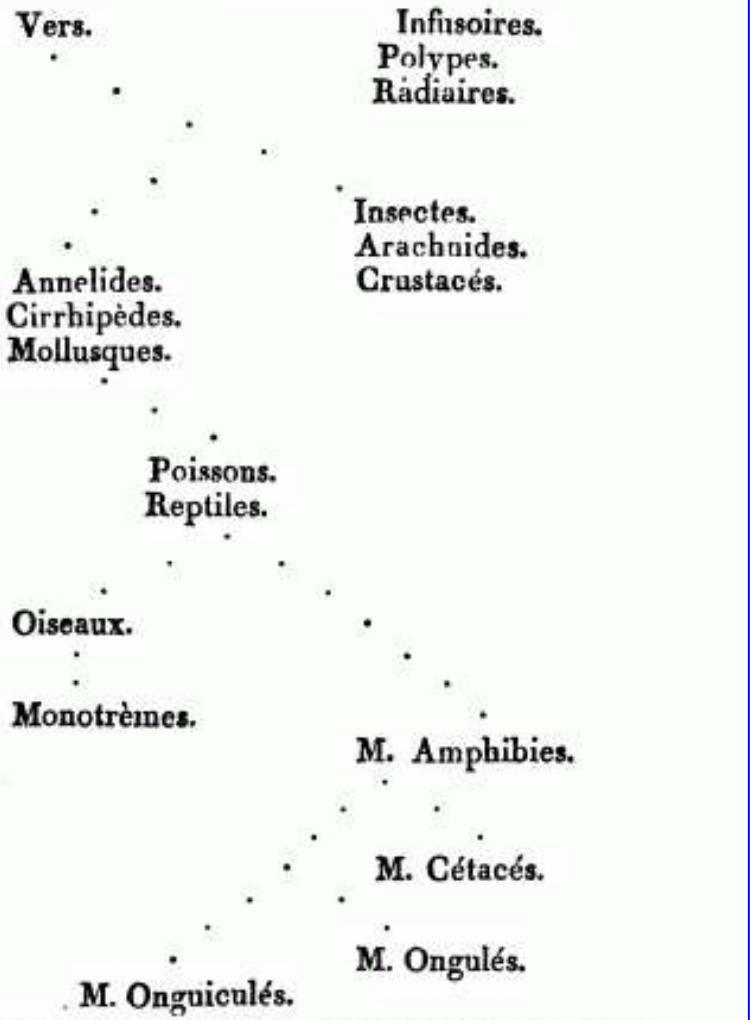
Georges-Louis Leclerc de Buffon, 1749

because *"nature, proceding by unknown gradations, cannot wholly lend herself to divisions. … In general, the more one increases the number of one's divisions, in the case of products of nature, the closer one comes to the truth, since in reality individuals alone exist in nature."*

ADDITIONS. 463

TABLEAU

Servant à montrer l'origine des différens animaux.



Cette série d'animaux commençant par deux

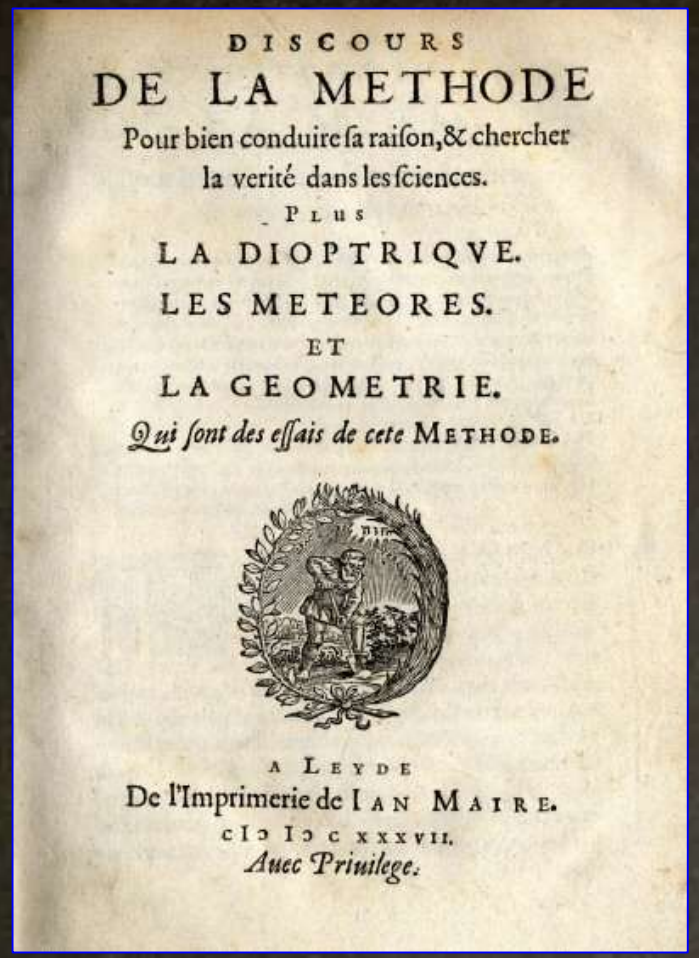
Jean-Baptiste de Lamarck
1744-1829

All classifications are arbitrary products of thought; … in nature there are only individuals.

Jean-Baptiste de Lamarck, 1809

Likewise, Buffon's pupil Jean-Baptiste Lamarck, the first to emphasize the gradual development of species, asserted in 1809 that *"all classifications are arbitrary products of thought … in nature there are only individuals."*

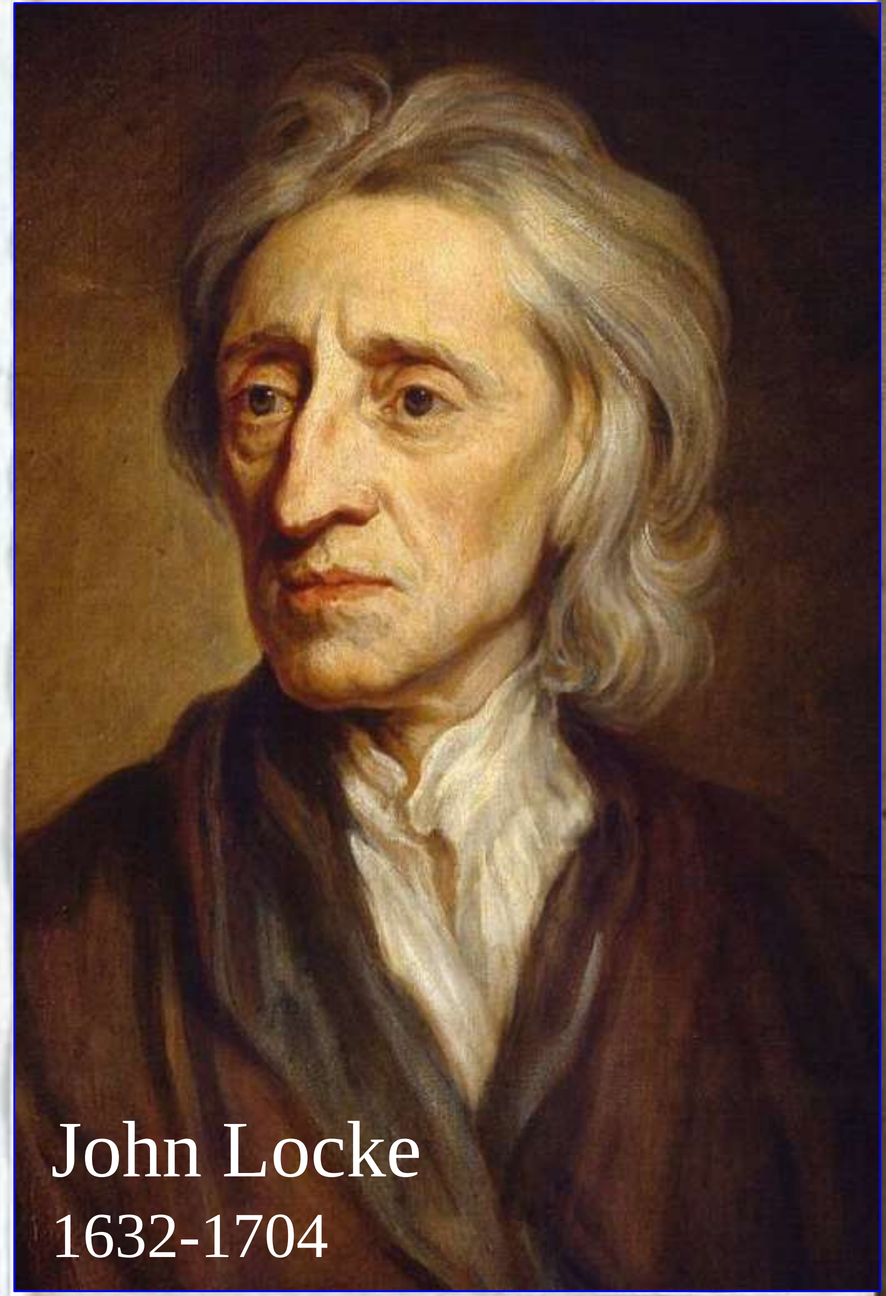
René Descartes
1596-1650

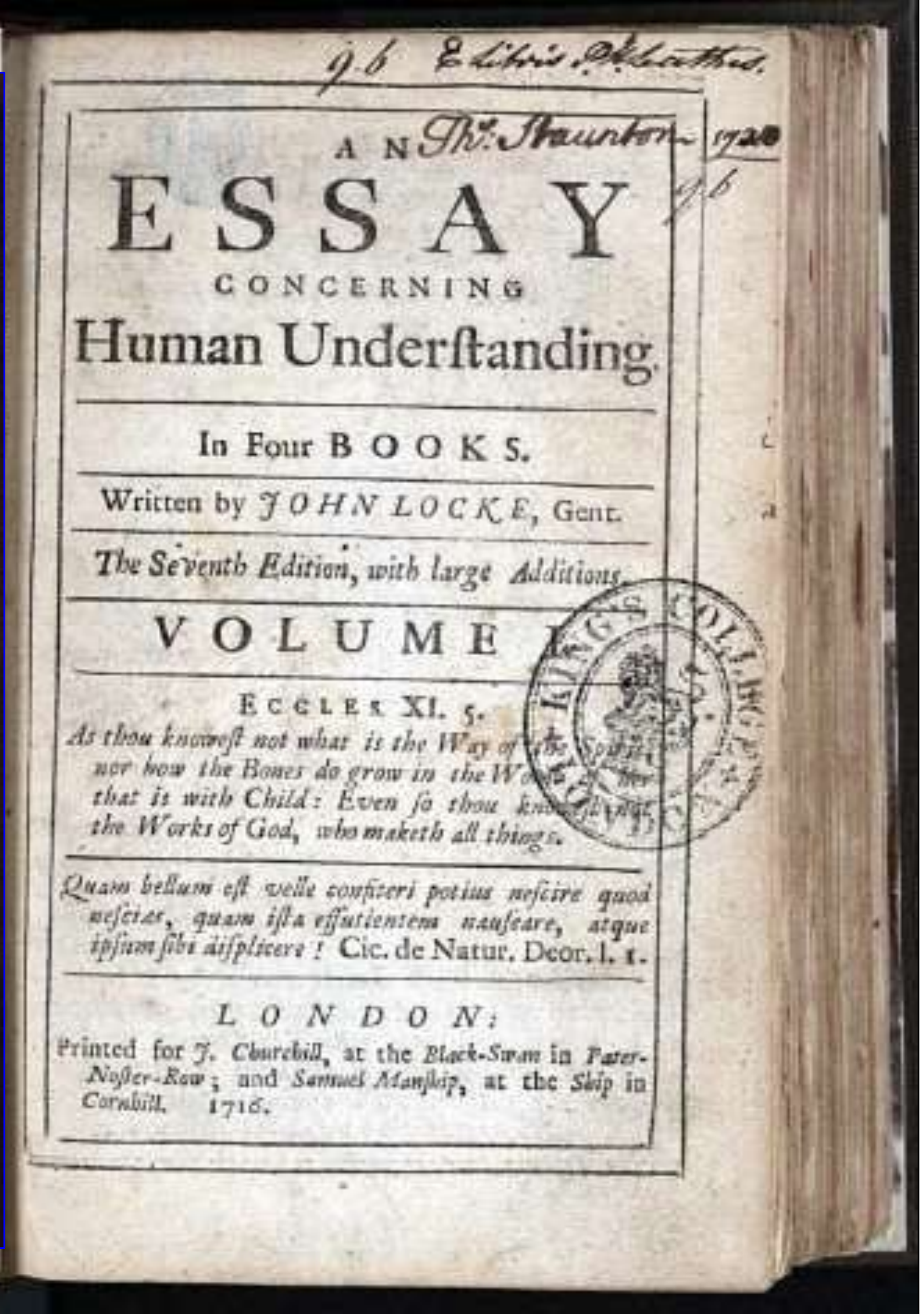

DISCOURS
DE LA METHODE
Pour bien conduire ſa raiſon,& chercher
la verité dans les ſciences.
PLUS
LA DIOPTRIQVE.
LES METEORES.
ET
LA GEOMETRIE.
Qui ſont des eſſais de cete METHODE.

A LEYDE
De l'Imprimerie de IAN MAIRE.
cIↃ IↃ c XXXVII.
Auec Priuilege.

Cogito ergo sum.

That point of view had a philosophical foundation that went back to René Descartes whose philosophy was based on methodological skepticism. He doubted anything perceived through the senses and believed that the only thing to be sure of was one's own mind, an idea casted in the famous proverb, "Cogito ergo sum." The conviction that conclusions about the material world could only be reached by the intellect meant, in reverse, that those conclusions were regarded as "products of thought." This influenced the concept of species.





AN
ESSAY
CONCERNING
Human Underſtanding.

In Four BOOKS.

Written by JOHN LOCKE, Gent.

The Seventh Edition, with large Additions.

VOLUME I.

ECCLES XI. 5.
As thou knoweſt not what is the Way of the Spirit, nor how the Bones do grow in the Womb of her that is with Child: Even ſo thou knoweſt not the Works of God, who maketh all things.

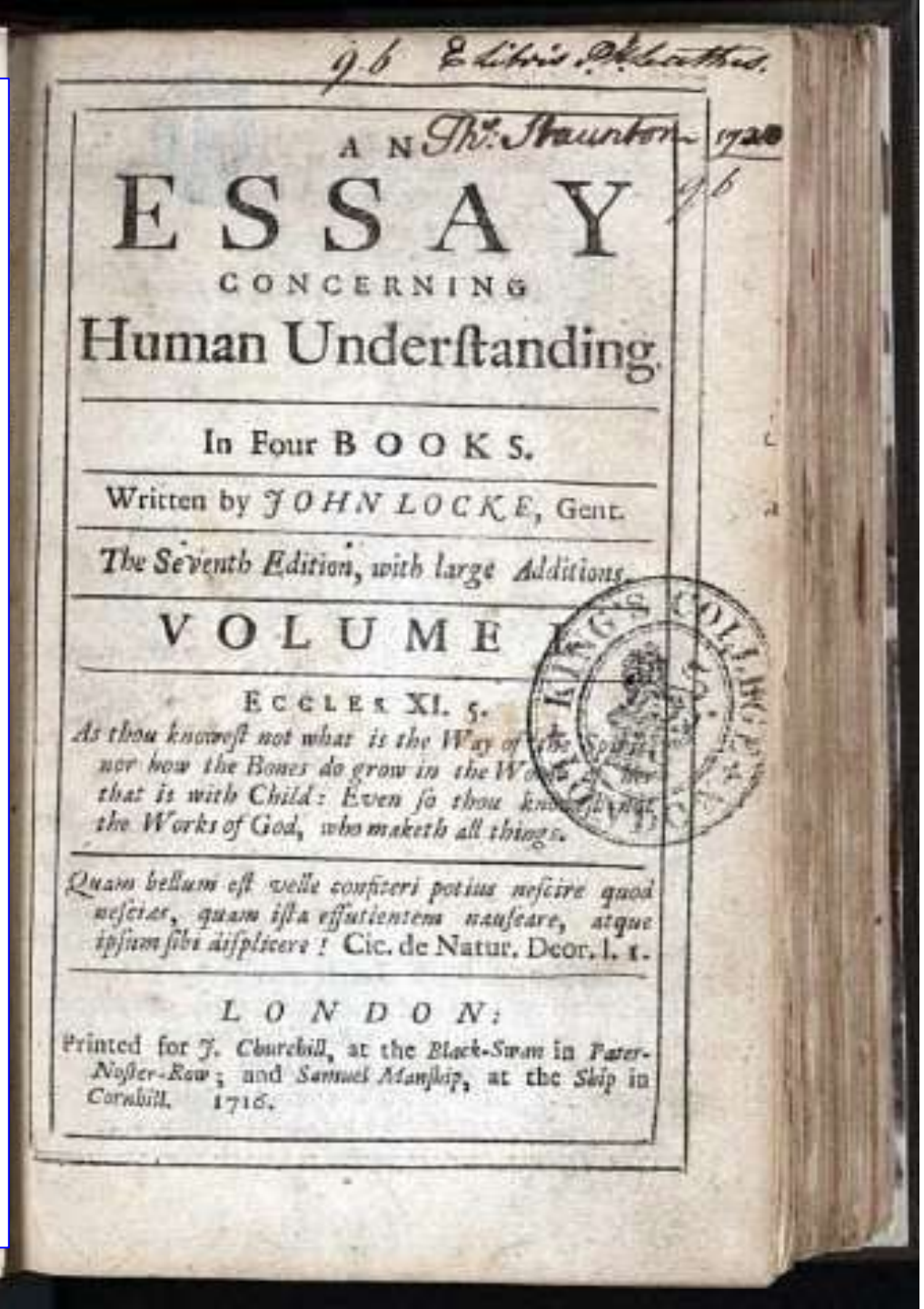
Quam bellum eſt velle confiteri potius neſcire quod neſcias, quam iſta effutientem nauſeare, atque ipſum ſibi diſplicere! Cic. de Natur. Deor. l. 1.

LONDON:
Printed for *J. Churchill*, at the *Black-Swan* in *Pater-Noſter-Row*; and *Samuel Manſhip*, at the *Ship* in *Cornhill*. 1716.

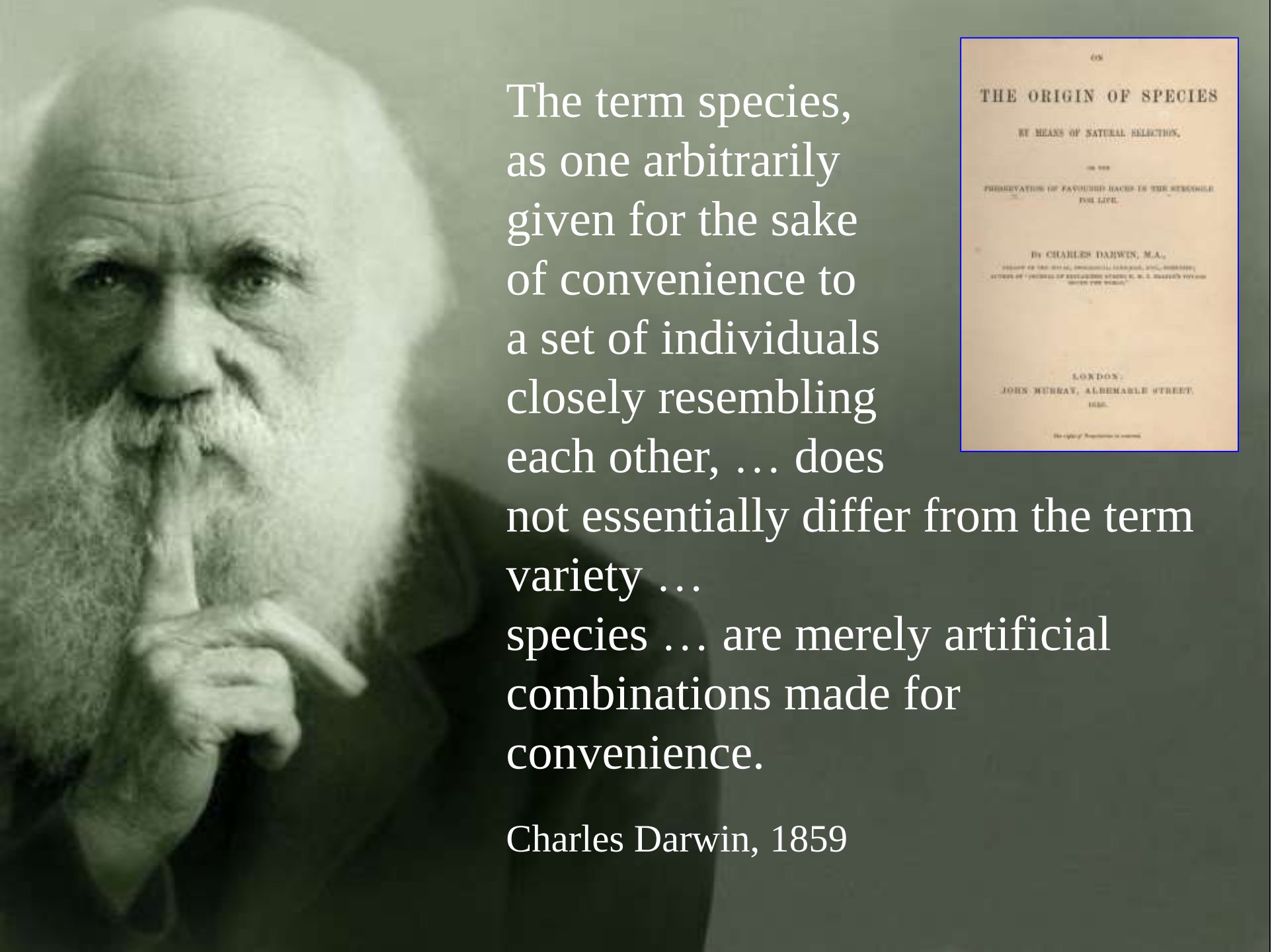
For example, English philosopher John Locke claimed, in his “Essay concerning human understanding” in 1690,

Nature makes many particular things which do agree with one another, in many sensible qualities …: but … it is men, who, taking occasion from the qualities they find united in them, … range them into sorts, in order to their naming, … under which individuals, according to their conformity to this or that abstract idea, come to be ranked as under ensigns …: and in this, I think, consists the whole business of genus and species.

John Locke, 1690



that "*nature makes many particular things which do agree with one another, in many sensible qualities … but … it is men, who, taking occasion from the qualities they find united in them, … range them into sorts, in order to their naming, … under which individuals, according to their conformity to this or that abstract idea, come to be ranked as under ensigns …: and in this, I think, consists the whole business of genus and species.*" Locke exerted a strong influence



The term species, as one arbitrarily given for the sake of convenience to a set of individuals closely resembling each other, … does not essentially differ from the term variety …
species … are merely artificial combinations made for convenience.

Charles Darwin, 1859

ON

THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

OR THE

PRESERVATION OF FAVOURED RACES IN THE STRUGGLE FOR LIFE.

By CHARLES DARWIN, M.A.,

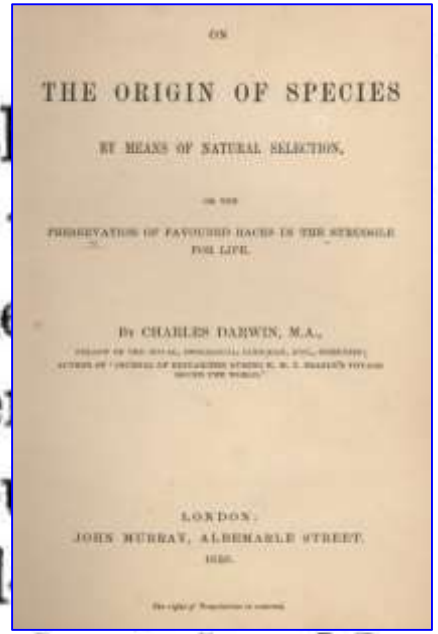
LONDON:
JOHN MURRAY, ALBEMARLE STREET.

on Charles Darwin who stated, in his landmark book, “On the origin of species by means of natural selection,” in 1859 that *“the term species, as one arbitrarily given for the sake of convenience to a set of individuals closely resembling each other, … does not essentially differ from the term variety … species … are merely artificial combinations made for convenience.”*

Despite that claim, Darwin was not a nominalist. He acknowledged not to be able to draw a firm line between species and varieties,

quickly than the small holders on the
narrow, hilly tract; and consequently t
mountain or plain breed will soon take
the less improved hill breed; and thus th
which originally existed in greater numbe
into close contact with each other, witho
position of the supplanted, intermediate hill

To sum up, I believe that species come to be tolerably well-defined objects, and do not at any one period present an inextricable chaos of varying and intermediate links: firstly, because new varieties are very slowly formed, for variation is a very slow process, and natural selection can do nothing until favourable variations chance to occur, and until a place in the natural


ON

THE ORIGIN OF SPECIES

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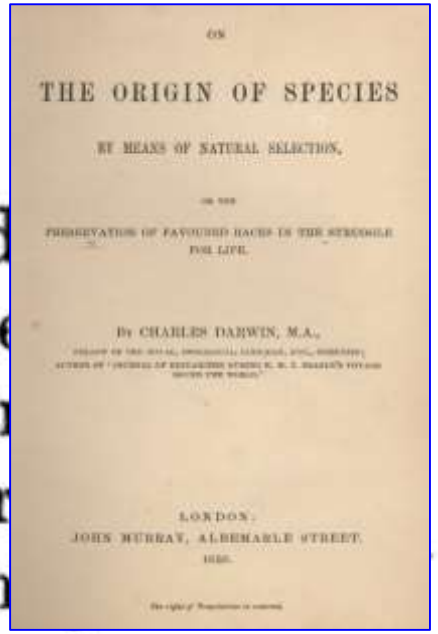
but he believed that *"species come to be tolerably well defined objects, and do not at any one period present an inextricable chaos of varying and intermediate links."* He also noted

All the foregoing rules and aids and d
classification are explained, if I do not gr
myself, on the view that the natural syste
on descent with modification; that the char
naturalists consider as showing true affin
any two or more species, are those which have been inherited from a common parent, and, in so far, all true classification is genealogical; that community of descent is the hidden bond which naturalists have been unconsciously seeking, and not some unknown plan of creation, or the enunciation of general propositions, and the mere putting together and separating objects more or less alike.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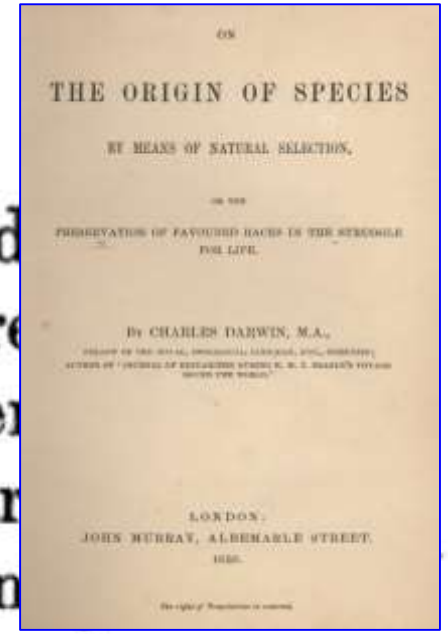
that *"community of descent is the hidden bond which naturalists have been unconsciously seeking"* and which distinguished an arbitrary classification from a "Natural System" because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"all true classification is genealogical."

The issue whether species actually existed in nature continued to be controversial,

Nature produces individuals and nothing more … species have no actual existence in nature … [but] have been invented in order that we may refer to great numbers of indivi-duals collectively.

Charles Edwin Bessey, 1908

and as late as in 1908, American botanist Charles Edwin Bessey stated categorically that *"nature produces individuals and nothing more … species have no actual existence in nature … [but] have been invented in order that we may refer to great numbers of individuals collectively."*

Eventually, however, it became accepted that species are more than *"artificial combinations made for convenience."*

Although they evolve through series of varieties that become reproductively isolated, they are separated from one another by bridgeless gaps, have internal coherence, and, within limits, continuity through time, their “eidos”



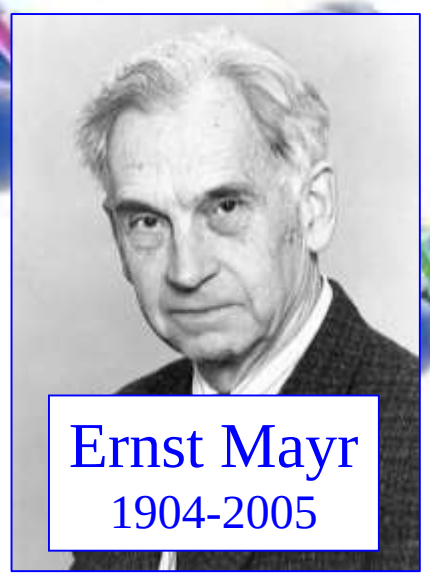





being a relatively stable genetic code. The latter, however, does not suffice to define them.

Systems almost always have the peculiarity that the characteristics of the whole cannot … be deduced from the most complete knowledge of the components.

Ernst Mayr, 1982

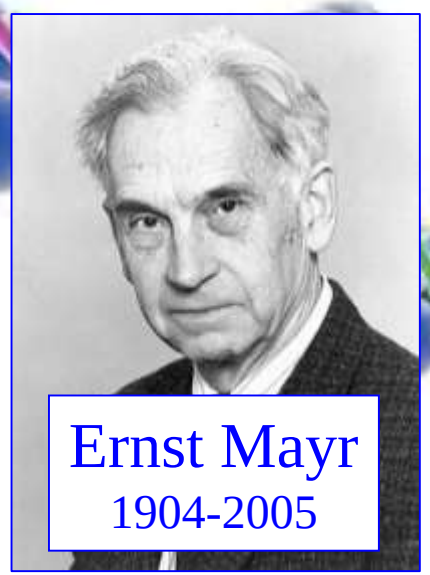


Ernst Mayr
1904-2005

As biologist Ernst Mayr pointed out, *"systems almost always have the peculiarity that the characteristics of the whole cannot … be deduced from the most complete knowledge of the components"* because new characteristics appear at higher levels of organization,

Systems almost always have the peculiarity that the characteristics of the whole cannot … be deduced from the most complete knowledge of the components.

Ernst Mayr, 1982



Ernst Mayr
1904-2005

Emergence

a phenomenon known as emergence.

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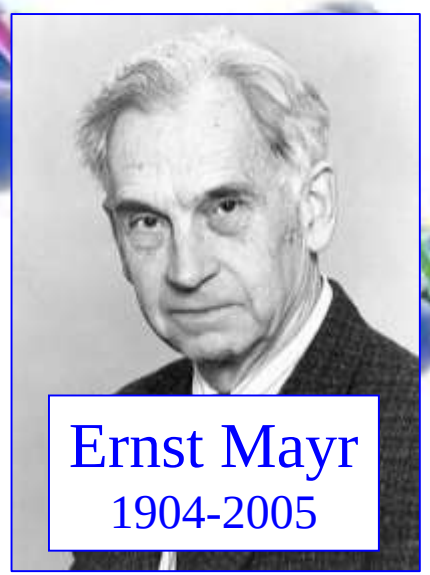
Emergence



Ernst Mayr
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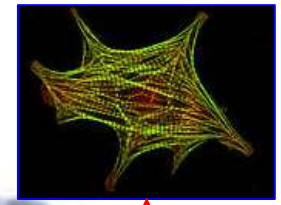
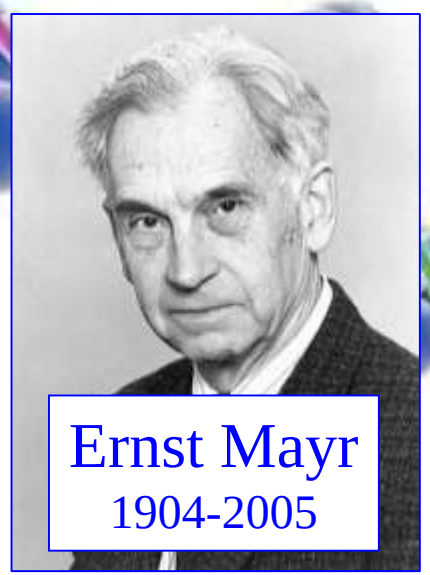


The genetic code does not explain all properties of the cell,

Systems almost always have the peculiarity that the characteristics of the whole cannot … be deduced from the most complete knowledge of the components.

Ernst Mayr, 1982



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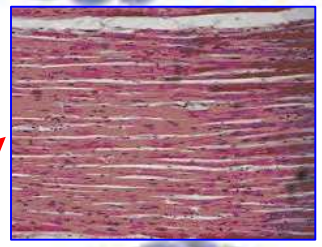
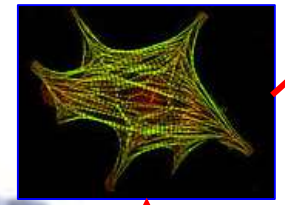
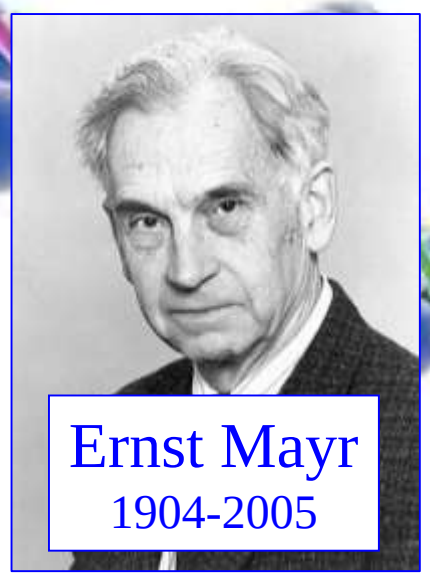




the individual cell not all properties of a tissue,

Systems almost always have the peculiarity that the characteristics of the whole cannot … be deduced from the most complete knowledge of the components.

Ernst Mayr, 1982



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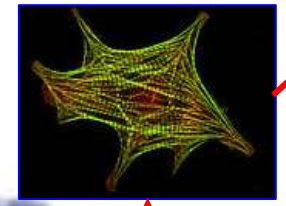

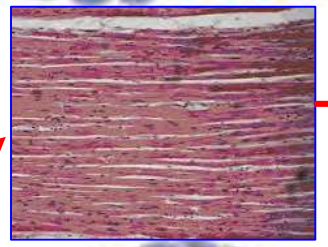

the tissue not all properties of an organ,

Systems almost always have the peculiarity that the characteristics of the whole cannot … be deduced from the most complete knowledge of the components.

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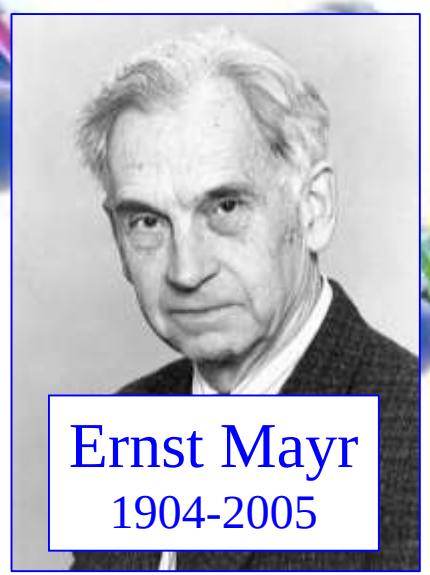
Emergence



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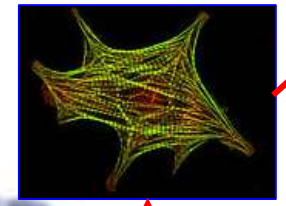
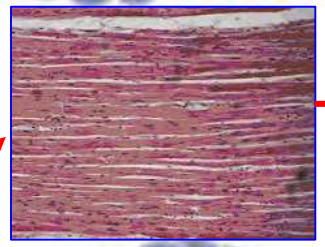
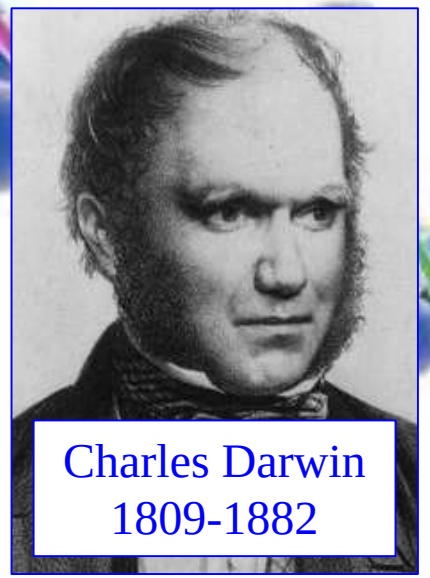




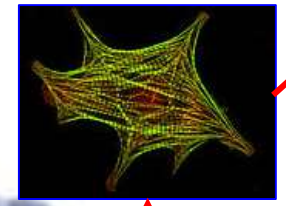
and the organ not the entire organism and its behavior.

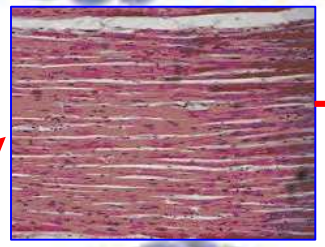
The value … of an aggregate of characters is very evident. … a classification founded on any single character, however important that may be, has always failed.

Charles Darwin, 1859



Charles Darwin
1809-1882

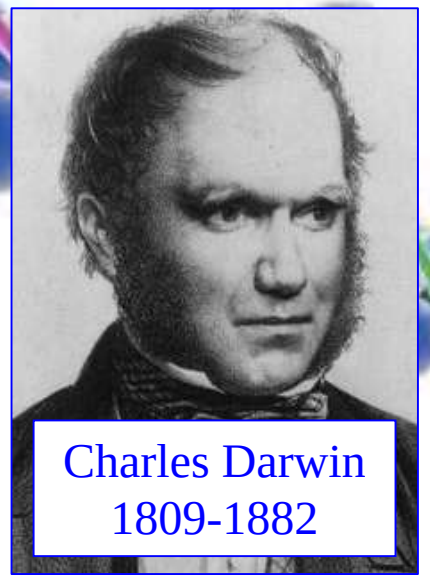




Already Darwin emphasized *"the importance of an aggregate of characters"* for classification and pointed out that *"a classification founded on any single character, however important that may be, has always failed."*

The value … of an aggregate of characters is very evident. … a classification founded on any single character, however important that may be, has always failed.

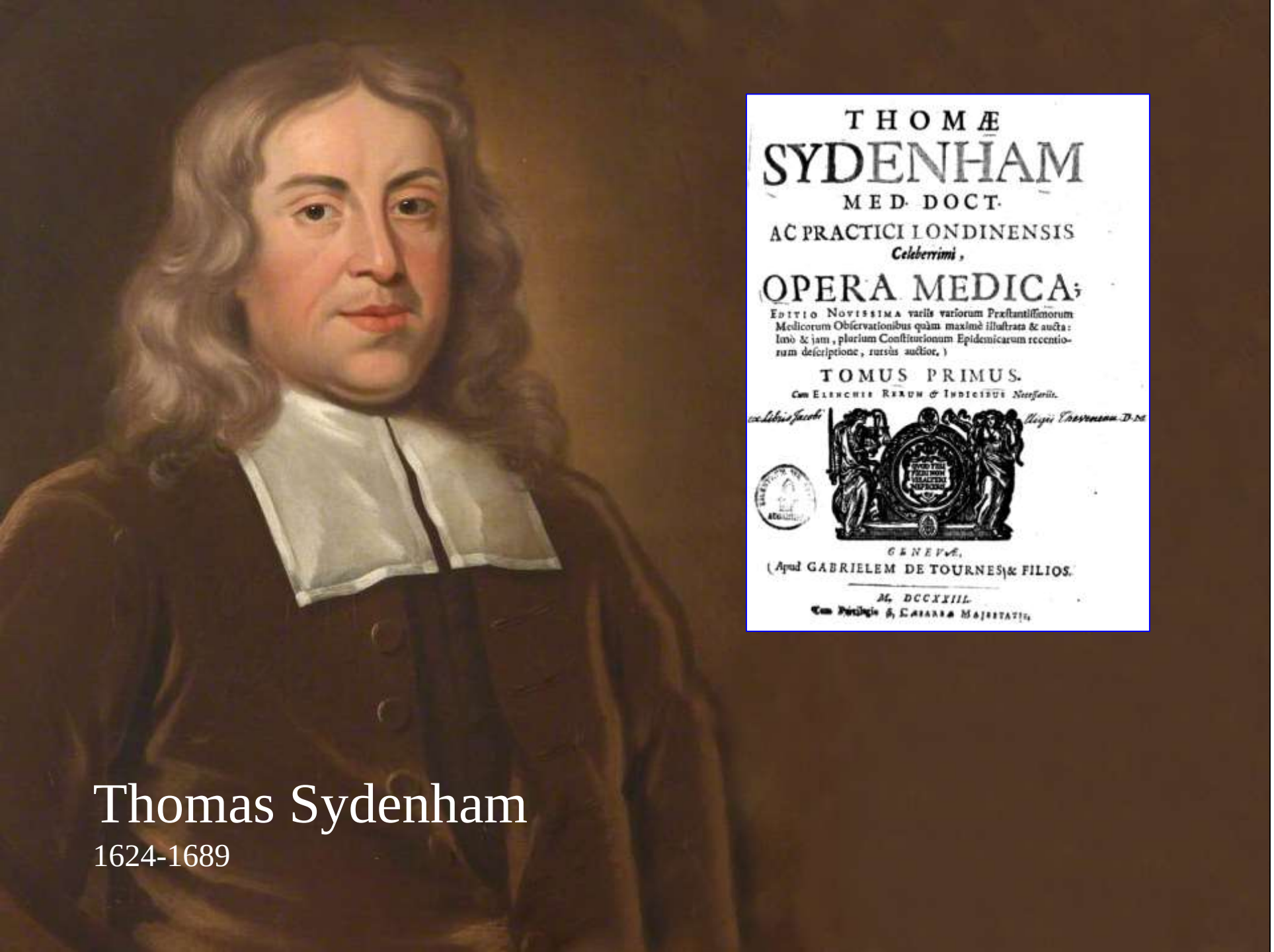
Charles Darwin, 1859



Charles Darwin
1809-1882

- reproductive isolation
  capability of reproducing fertile offspring
- morphology, niche occupation, metabolism, genetics
- marying importance of criteria
- combination of criteria
- correlation of criteria

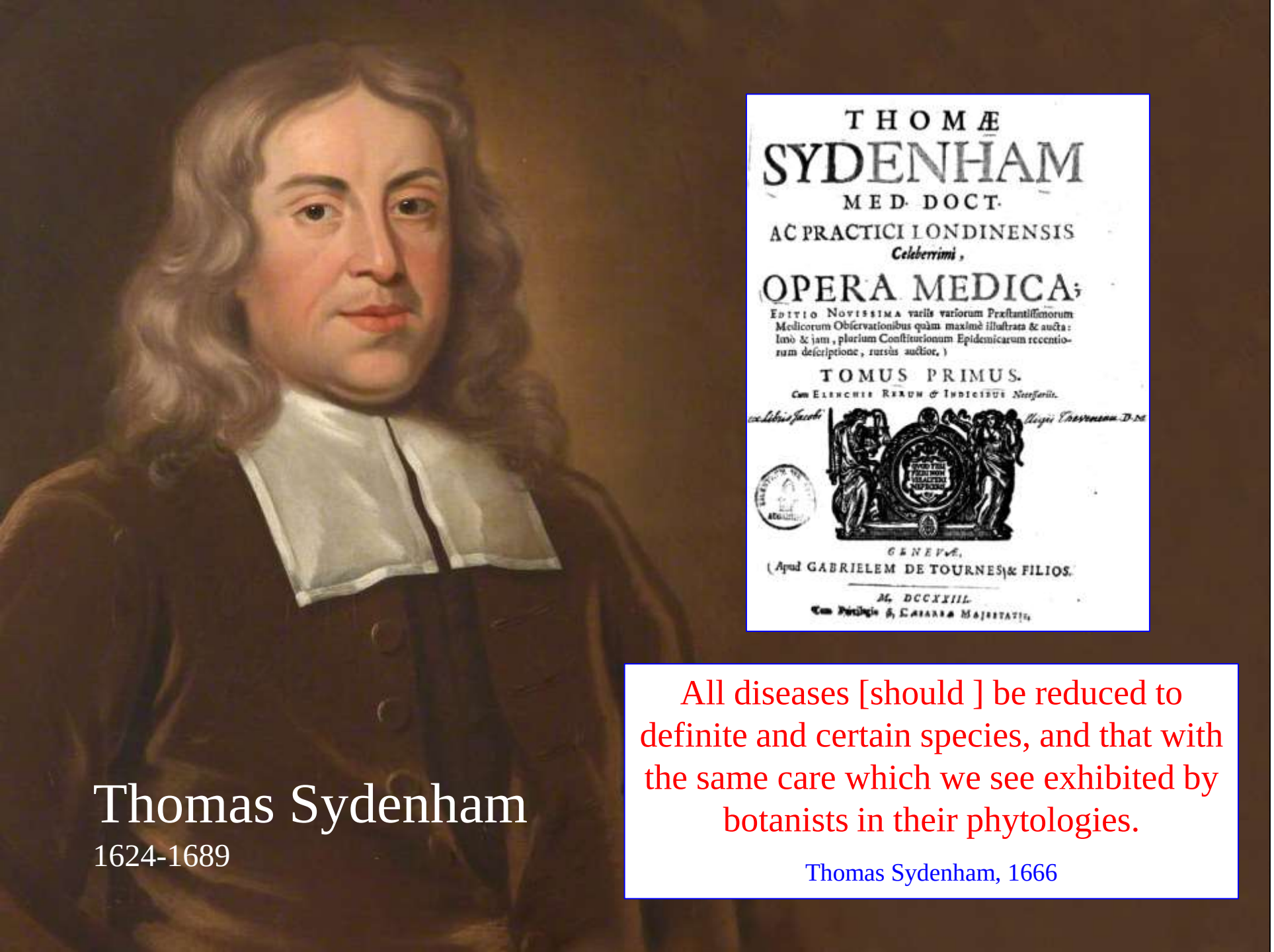
Accordingly, species are currently defined by clusters of correlated variables, including reproductive isolation with the capability of reproducing fertile offspring, morphology, niche occupation, metabolism, and genetics. The taxonomic importance of criteria varies from species to species, and there is agreement that a combination of criteria is essential and that the latter should correlate with one another.



Thomas Sydenham
1624-1689

THOMÆ
SYDENHAM
MED. DOCT.
AC PRACTICI LONDINENSIS
Celeberrimi,
OPERA MEDICA;
EDITIO NOVISSIMA variis variorum Præstantissimorum Medicorum Observationibus quàm maximè illustrata & aucta: Imò & jam, plurium Constitucionum Epidemicarum recentiorum descriptione, rursùs auctior.)
TOMUS PRIMUS.
Cum ELENCHIS RERUM & INDICIBUS Necessariis.
GENEVÆ,
(Apud GABRIELEM DE TOURNES & FILIOS.
M. DCC.XXIII.
Cum Privilegio S. Cæsareæ Majestatis.

Let us now return to medicine were the same issues have been discussed since the mid 17th century when the so-called “English Hippocrates,” Thomas Sydenham, demanded



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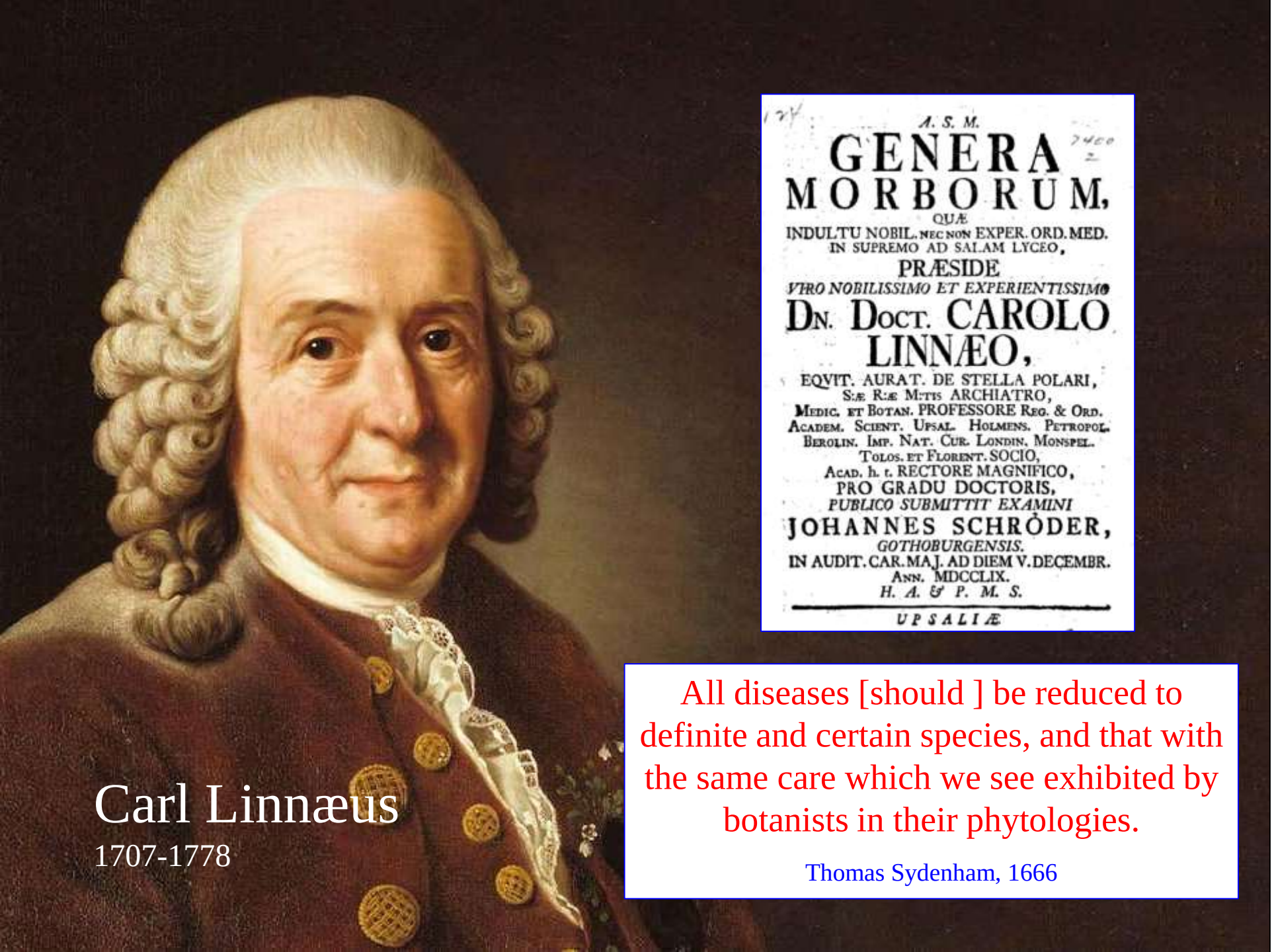
GENEVÆ,
(Apud GABRIELEM DE TOURNES & FILIOS.
M. DCC.XXIII.
Cum Privilegio S. Cæsareæ Majestatis.

All diseases [should] be reduced to definite and certain species, and that with the same care which we see exhibited by botanists in their phytologies.

Thomas Sydenham, 1666

that *"all diseases be reduced to definite and certain species, and that, with the same care which we see exhibited by botanists in their phytologies."* Sydenham's challenge was soon accepted by physicians,



Carl Linnæus
1707-1778

A. S. M.

GENERA MORBORUM,

QUÆ

INDULTU NOBIL. NEC NON EXPER. ORD. MED.
IN SUPREMO AD SALAM LYCEO,

PRÆSIDE

VIRO NOBILISSIMO ET EXPERIENTISSIMO

DN. DOCT. CAROLO LINNÆO,

EQVIT. AURAT. DE STELLA POLARI,
S:Æ R:Æ M:TIS ARCHIATRO,
MEDIC. ET BOTAN. PROFESSORE REG. & ORD.
ACADEM. SCIENT. UPSAL. HOLMENS. PETROPOL.
BEROLIN. IMP. NAT. CUR. LONDIN. MONSPEL.
TOLOS. ET FLORENT. SOCIO,
ACAD. h. t. RECTORE MAGNIFICO,
PRO GRADU DOCTORIS,
PUBLICO SUBMITTIT EXAMINI

JOHANNES SCHRÖDER,

GOTHOBURGENSIS.

IN AUDIT. CAR. MAJ. AD DIEM V. DECEMBR.
ANN. MDCCLIX.
H. A. & P. M. S.

UPSALIÆ

All diseases [should] be reduced to definite and certain species, and that with the same care which we see exhibited by botanists in their phytologies.

Thomas Sydenham, 1666

including Carl Linnæus himself who supplemented his “Systema naturae” by a “Genera morborum.”

François Boissier de Sauvages de la Croix

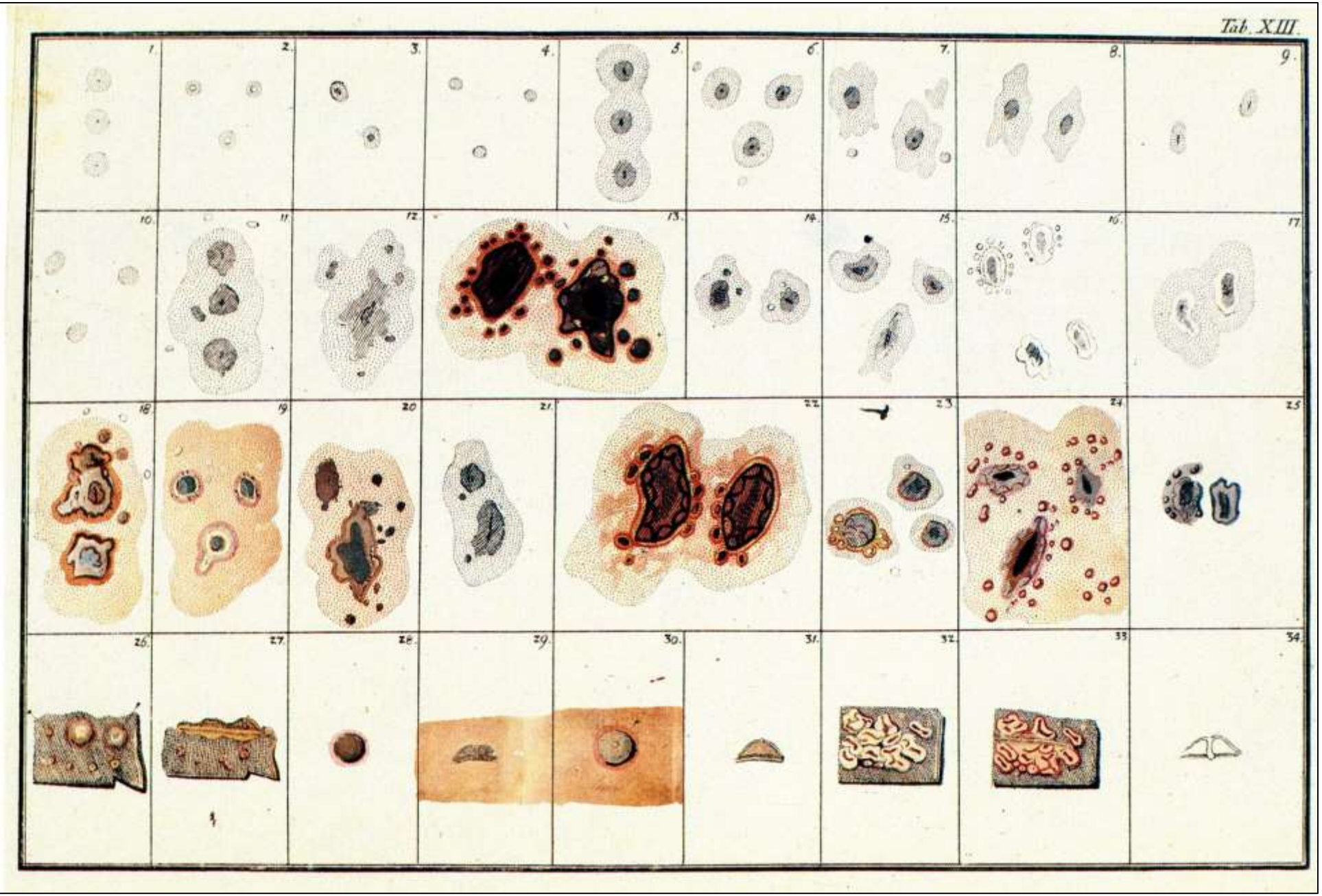
1706-1767

NOSOLOGIA METHODICA
SISTENS
MORBORUM CLASSES
Juxtà Sydenhami mentem & Botanicorum ordinem.
AUCTORE
FRANCISCO BOISSIER DE SAUVAGES
Regis Consiliario ac Medico, in Monspeliensi Universitate Medicinæ, olimque Botanices, Professore Regio; Academiæ Scientiarum Monspeliensis, Londinensis, Upsaliensis, Berolinensis, Florentinæ, Physico-Botanicæ, Suecicæ, Naturæ curiosorum, & Instituti Bononiensis Socio.
Editio ultima, auctior, & emendatior.
TOMUS PRIMUS.
Si morbi cujuslibet historiam diligenter perspectam haberem, par malo remedium nunquam non istorum adfero. Sydenham.
AMSTELODAMI,
Sumptibus FRATRUM DE TOURNES.
MDCCLXVIII.

All diseases [should] be reduced to definite and certain species, and that with the same care which we see exhibited by botanists in their phytologies.

Thomas Sydenham, 1666

One of his friends, French physician François Boissier de Sauvages, presented an ambitious classification of diseases *"in the spirit of Sydenham and the order of botanists,"* eventually distinguishing 10 classes with 44 orders, more than 300 genera, and 2,400 species. In his endeavor to identify an essential sign or symptom for each disease,



skin lesions such as macules, papules, and pustules played an important role. Although the classification was highly inconsistent and even admirers referred to it as *“a sort of nosological bazaar,”* the approach proved fruitful.

DESCRIPTION AND TREATMENT

OF

CUTANEOUS DISEASES.

ORDER I.

PAPULOUS ERUPTIONS

ON THE

SKIN.

BY

ROBERT WILLAN, M.D. F.A.S.

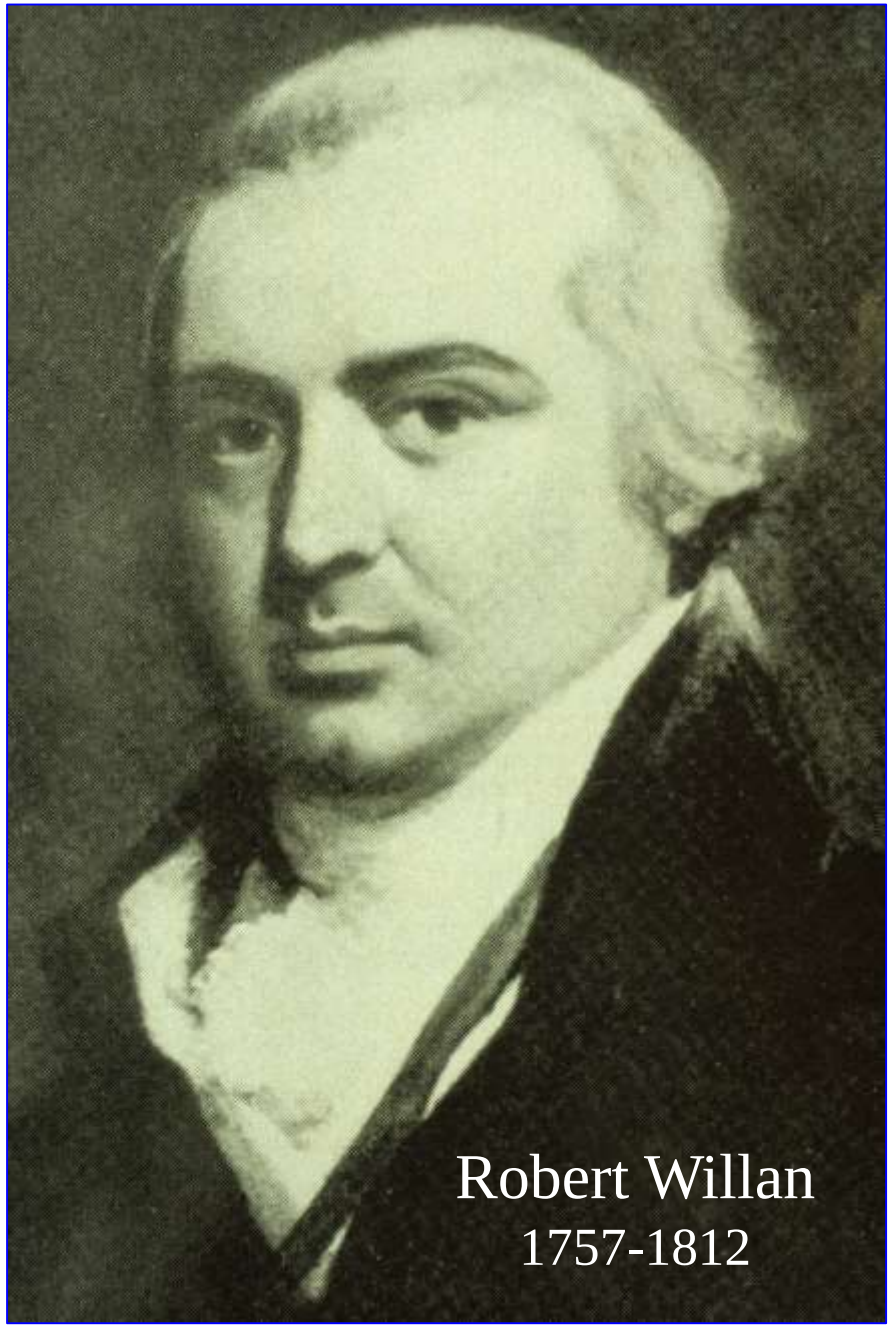
LONDON:

PRINTED FOR J. JOHNSON, ST. PAUL'S CHURCH-YARD.

1798.

TO THE PUBLICK.

IN conducting the following Work, it is propoſed to publiſh the ſeven Orders, of which it conſiſts, ſeparately. The Orders, as ſtated Page 16, are characterized by the different Appearances



Robert Willan
1757-1812

It was adopted by Robert Willan of London whose classification of skin diseases based on *"the different Appearances"* marked the beginning of modern dermatology.

Definitions page 12.

ORDER I.

PAPULÆ. Page

STROPHULUS 1
LICHEN 6
PRURIGO 14

II.

SQUAMÆ.

LEPRA 25
PSORIASIS 36
PITYRIASIS 45
ICHTHYOSIS 49

III.

EXANTHEMATA.

RUBEOLA 56
SCARLATINA 69
URTICARIA 87
ROSEOLA 96
PURPURA 103
ERYTHEMA 118

IV.

BULLÆ.

ERYSIPELAS 125
PEMPHIGUS 136
POMPHOLYX 139

V.

PUSTULÆ.

IMPETIGO 145
PORRIGO 159

Page

ECTHYMA 181
VARIOLA 189
SCABIES 190

VI.

VESICULÆ.

VARICELLA 207
VACCINIA 215
HERPES 221
RUPIA 240
MILIARIA 242
ECZEMA 250
APHTHA 260

VII.

TUBERCULA.

PHYMA 270
VERRUCA .. .. .. *ibid.*
MOLLUSCUM 271
VITILIGO 273
ACNE 275
SYCOSIS 291
LUPUS 295
ELEPHANTIASIS 297
FRAMBŒSIA 312

VIII.

MACULÆ.

EPHELIS 320
NÆVUS, SPILUS, ETC. .. 323

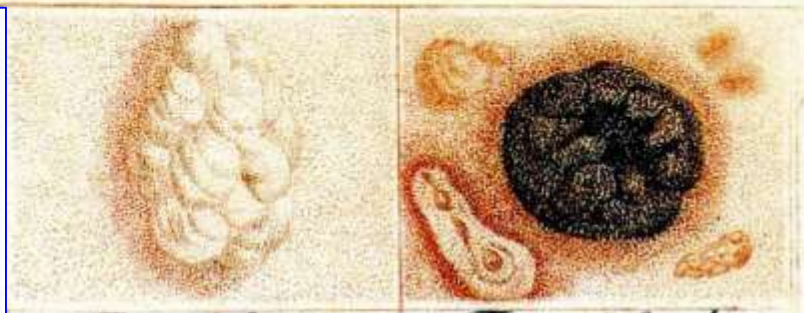


Fig. 3. Crust. Fig. 4. Scabs.

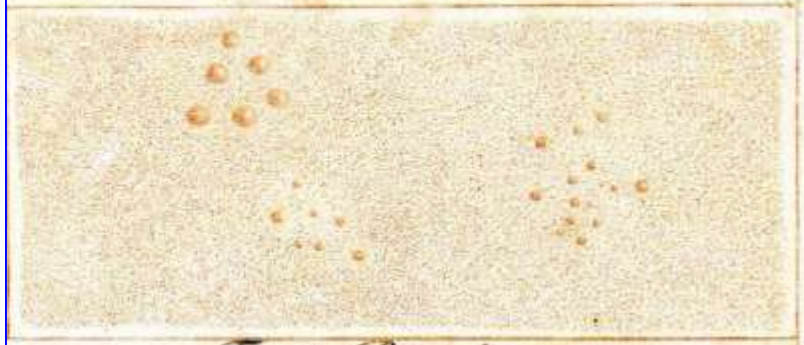
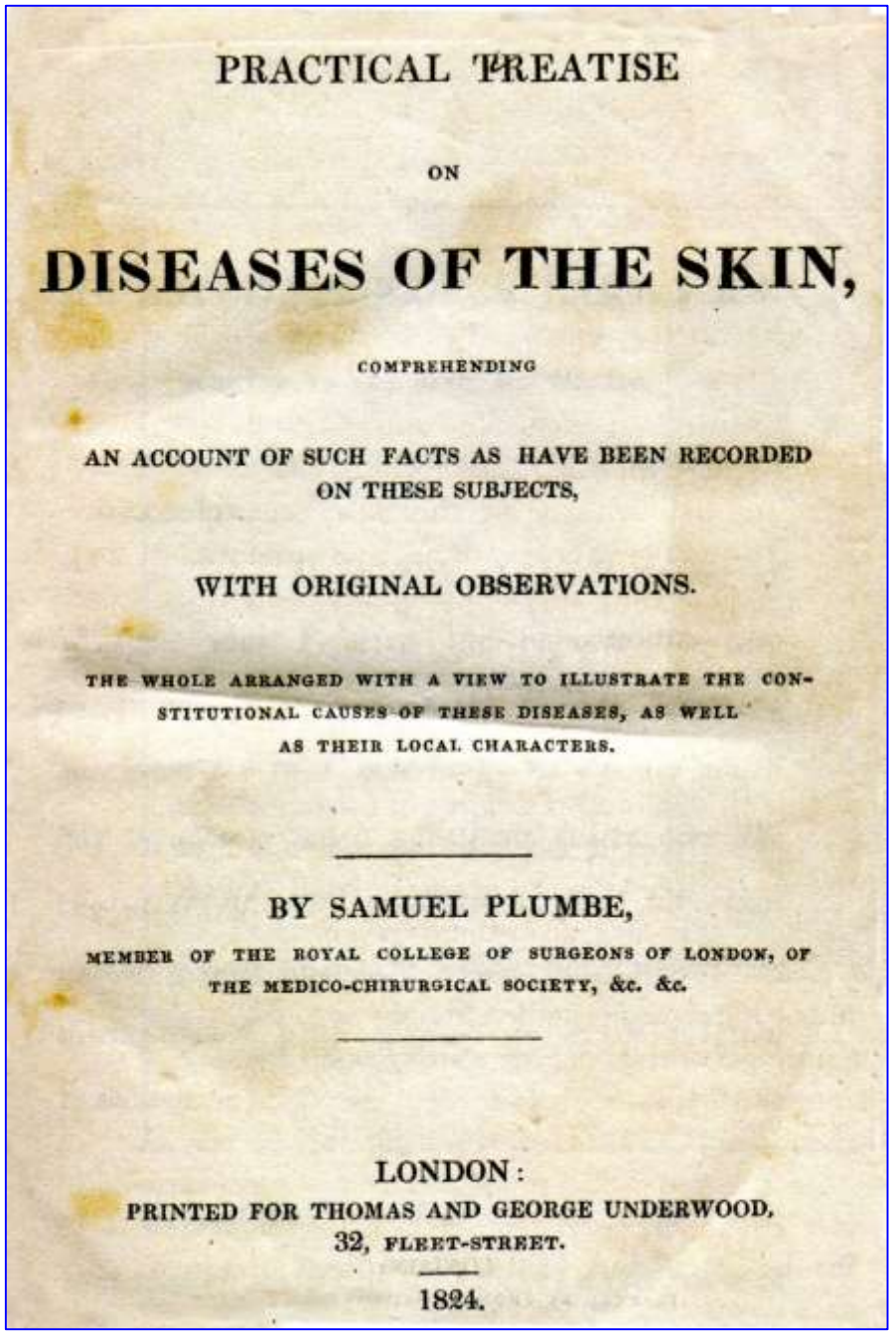


Fig. 6. Papulæ.

In the first volume of his work in 1798, Willan distinguished seven and later eight orders of diseases, each of which had a different predominating type of lesion. Willan was aware of combinations and transitions of different types of lesions but emphasized the value of the predominating one for the identification of diseases. Like Linnæus in his “Systema naturae,” he presented an identification scheme, rather than a biological classification, but that difference was not acknowlegded.

Samuel Plumbe
1795-1838



PRACTICAL TREATISE

ON

DISEASES OF THE SKIN,

COMPREHENDING

AN ACCOUNT OF SUCH FACTS AS HAVE BEEN RECORDED ON THESE SUBJECTS,

WITH ORIGINAL OBSERVATIONS.

THE WHOLE ARRANGED WITH A VIEW TO ILLUSTRATE THE CONSTITUTIONAL CAUSES OF THESE DISEASES, AS WELL AS THEIR LOCAL CHARACTERS.

BY SAMUEL PLUMBE,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS OF LONDON, OF THE MEDICO-CHIRURGICAL SOCIETY, &c. &c.

LONDON:
PRINTED FOR THOMAS AND GEORGE UNDERWOOD,
32, FLEET-STREET.

1824.

Deeply rooted in essentialism, most physicians tried to grasp the “essence” of diseases, and because the latter could not consist of the fluctuating elementary lesions,
Willan’s classification was citicized harshly by dermatologists like Samuel Plumbe who, in his “Practical Treatise on Diseases of the Skin” in 1824, proposed a classification based on cause. The cause, however, was unknown for nearly all diseases.

Classificationsübersicht.

Erste Klasse. Dermatonosen.

Erste Ordnung. Morphonosen der Haut.

I. Familie. Teratosen.

Erste Sippschaft. Dysmorphosen.

1. Gattung. Adermia.
2. — Albinismus.
3. — Atrichia.
4. — Anonychia.

C.H. Fuchs, 1840

I. Hyperaemiae cutaneae – Blutfülle der Haut,
II. Anaemiae cutaneae – Blutmangel der Haut,
III. Anomaliae secretionis glandularum cutanearum – krankhafte Absonderung der Hautdrüsen,
IV. Exsudationes – Ausschwitzungen,
V. Hämorragiae cutaneae – Blutaustretungen,
VI. Hypertrophiae – Massenzunahme,
VII. Atrophiae – Massenverminderung,
VIII. Neoplasmata (Homeoplasiae) - gutartige Neubildungen,
IX. Pseudoplasmata (Heteroplasiae) - bösartige Neubildungen,
X. Ulcerationes – Verschwärungen,
XI. Neuroses – Neurosen – Nervenkrankheiten,
XII. Parasitae – Schmarotzer-Hautkrankheiten.

F. Hebra, 1845

VI. Klasse.
Regressive Ernährungsstörungen.

A. Der Cutis und Subcutis.	B. Der Drüsen.	C. Der Haare.	D. Der Nägel.	E. Des Pigments.
1. **Atrophiae** a. Atrophia congenita. b. Atrophia senilis. c. Atrophia traumatica. d. Sklerodermia adultorum. e. Xerodermie. α. Xeroderma simplex. β. Xeroderma pigmentosum. f. Glossy Skin Sklerodaktylie. g. Cutis laxa. h. Kraurosis vulvae. 2. **Degeneration** a. Myxödem. b. Sklerema neonatorum. 3. **Nekrose** Noma. Gangraena senilis. Gangraena diabetica. Gangraena multiplex cachecticorum. Gangraena symmetrica (Raynaud). Decubitus acutus. Malum perforans. Ainhum.	1. **Atrophie der Schweifsdrüsen.** 2. **Atrophie der Talgdrüsen.**	1. **Quantitative Atrophie der Haare.** a. Alopecia senilis et praematura. b. Alopecia areata. c. Alopecia furfuracea. 2. **Qualitative Atrophie der Haare.** a. Änderung der Gestalt. Scissura. Trichorrhexis nodosa. Aplasia moniliformis. b. Änderungen der Farbe. Canities. Pili annulati. Farbenwechsel.	1. Atrophia unguium a. congenita. b. acquisita. 2. Leukoma (Achroma).	1. **Albinismus congenitaler Pigmentmangel** universalis. circumscriptus. 2. **Vitiligo- Leukopathie erworbener Pigmentmangel.**

S. Jessner, 1893

I. Dermatitides simplices, Dermatosen mit dem Charakter der einfach entzündlichen Wallung.
II. Angioneurotische Dermatosen mit dem Charakter einer ausgedehnten Störung des Gefäßtonus neben mehr oder weniger ausgeprägter entzündlicher Wallung an der Hautoberfläche,
III. Neuritische Dermatosen, durch Erkrankung sensibler-trophischer Nerven,
IV. Stauungsdermatosen, passive Cirkulationsstörung und beeinträchtigte, venös-lymphatische Aufsaugung,
V. Hämorrhagische Dermatosen, gesteigerter Durchtritt roter Blutkörperchen durch die Gefäßwände ohne entzündliche Wallung und lokale Stase,
VI. Idioneurosen, Funktionsstörungen der Hautnerven ohne trophische Störungen entzündlicher oder vasomotorischer Natur und ohne Wachstumsstörungen,
VII. Epidermidosen, Wachstumsanomalieen der Oberhaut und ihrer Anhangsgebilde (Keratonosen, Chromatosen, Akanthosen).
VIII. Chorioblastosen (Hyper-, Para-, Adesmosen),
IX. Mykosen (favosa, circinata, pustulosa, furfuracea).

H. Auspitz, 1881

Numerous other classifications followed in which authors tried to arrange skin diseases according to a single aspect that was considered to be the most essential one. However, as in biology at large, the criteria for the definition of diseases vary from species to species. As a consequence, all such proposals were unsatisfactory until those attempts were abandoned

and some authors simply listed diseases in alphabetical order, as in the major French textbook of 1900, “La Pratique Dermatologique.”

The latter approach furthered a nominalistic attitude, i.e., the assumption that diseases were merely names without real existence in nature. That belief was already prevalent in biology and medicine.

I.

Die naturwissenschaftliche Methode und die Standpunkte in der Therapie.

Von Rud. Virchow.

(Gelesen bei der Jahressitzung der Gesellschaft für wissenschaftliche Medicin zu Berlin am 20. Decbr. 1847.)

Wenn wir an den Ausspruch des alten Asklepiaden denken, dafs das Leben kurz und die Kunst lang ist, so wundern wir uns nicht mehr über die hastige Eile, mit der der Einzelne darnach hascht, in dem kurzen Leben die ganze lange Kunst zu ergründen. Wie das alles drängt und stolpert! Jahrtautausende sind über dies Geschlecht von Sterblichen dahin gegangen, Keiner noch hat des Lebens Kern erfafst, Alle sind vor der Lösung des grofsen Räthsels zu Staub geworden und ihre Gräber predigen die Eine Wahrheit: *ne quid nimis.* Aber wer hat aus der Vergangenheit gelernt? für wen ist die Geschichte da? wo giebt es Erbweisheit? Jeder hat in seiner Zeit Alles sein wollen und hat darüber die Erblehre aller Vergangenheit vergessen, dafs nur das Streben nach Einem, bewufsten und erreichbaren Ziele, dafs nur das Fortbauen auf den sicheren und gekannten Grundlagen der Väter, dafs nur das Anschmiegen an das allmächtige Bewufstsein der Zeitgenossen einen grofsen, gewissen und dauerhaften Erfolg verspricht. Jeder hat einen neuen Tempelbau angefangen, neue

For example, the pioneer of cellular pathology, Rudolf Virchow adopted a strictly “anti-ontological” position.

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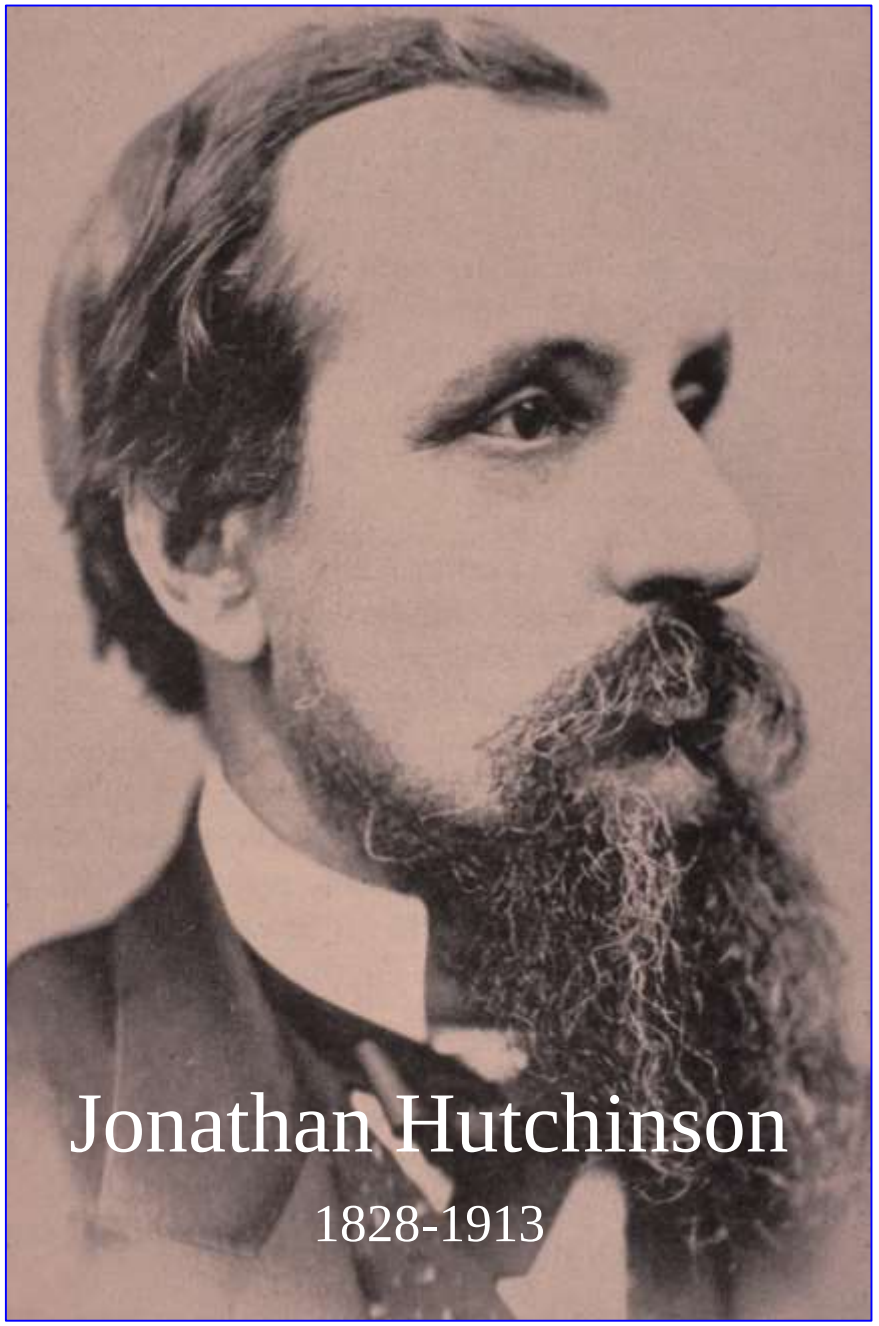
Disease is nothing but the regular manifestation of certain (principally normal) vital processes under unusual conditions.

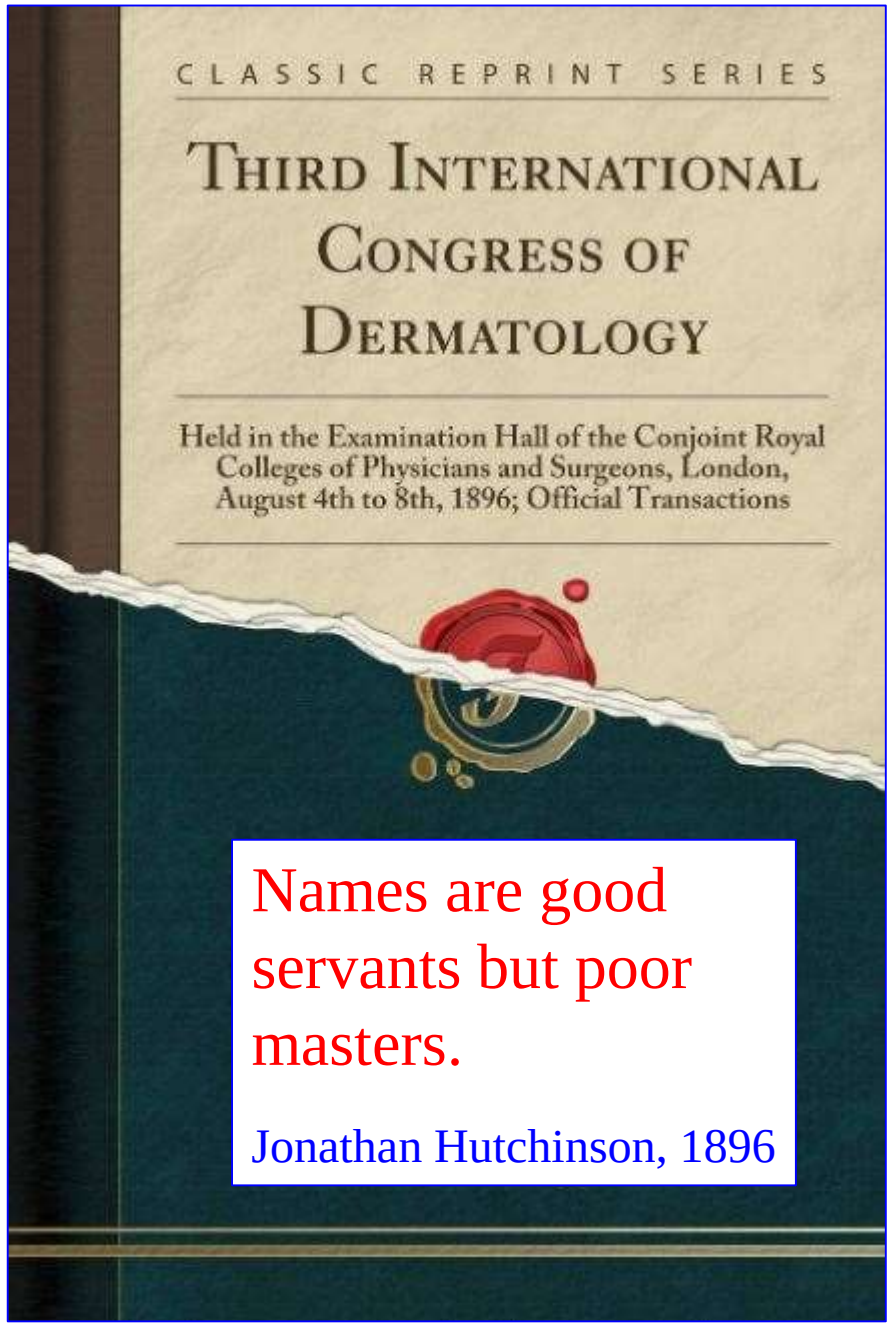
There are no disease entities.

Virchows Archiv 1849; 2: 3-37

Rudolf Virchow
1821-1902

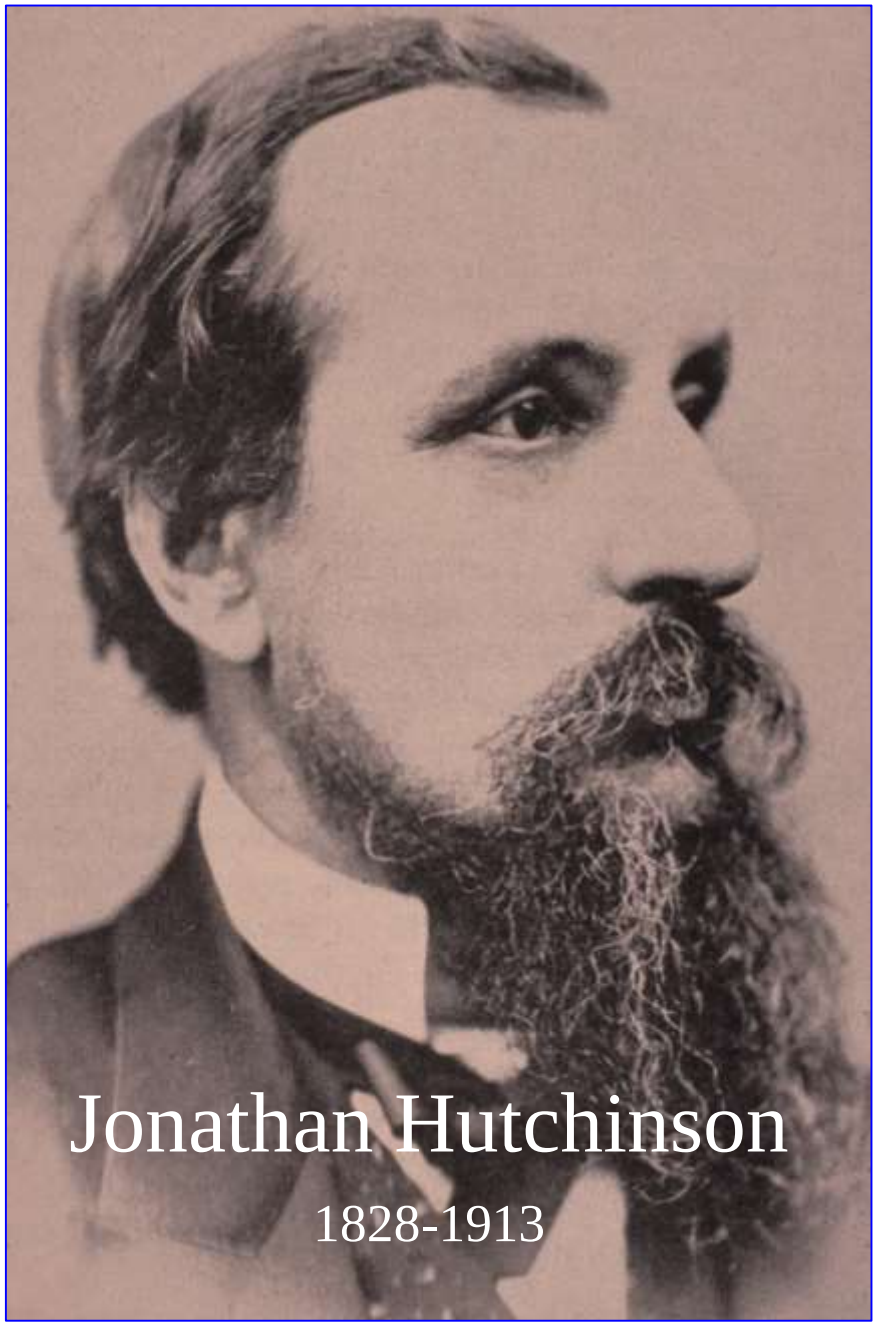
He claimed that *"disease is nothing but the regular manifestation of certain (principally normal) vital processes under unusual conditions"* and that *"there are no disease entities."*





At the third World Congress of Dermatology in London in 1896, Jonathan Hutchinson concluded a session with the remark, *"names are good servants but poor masters."*

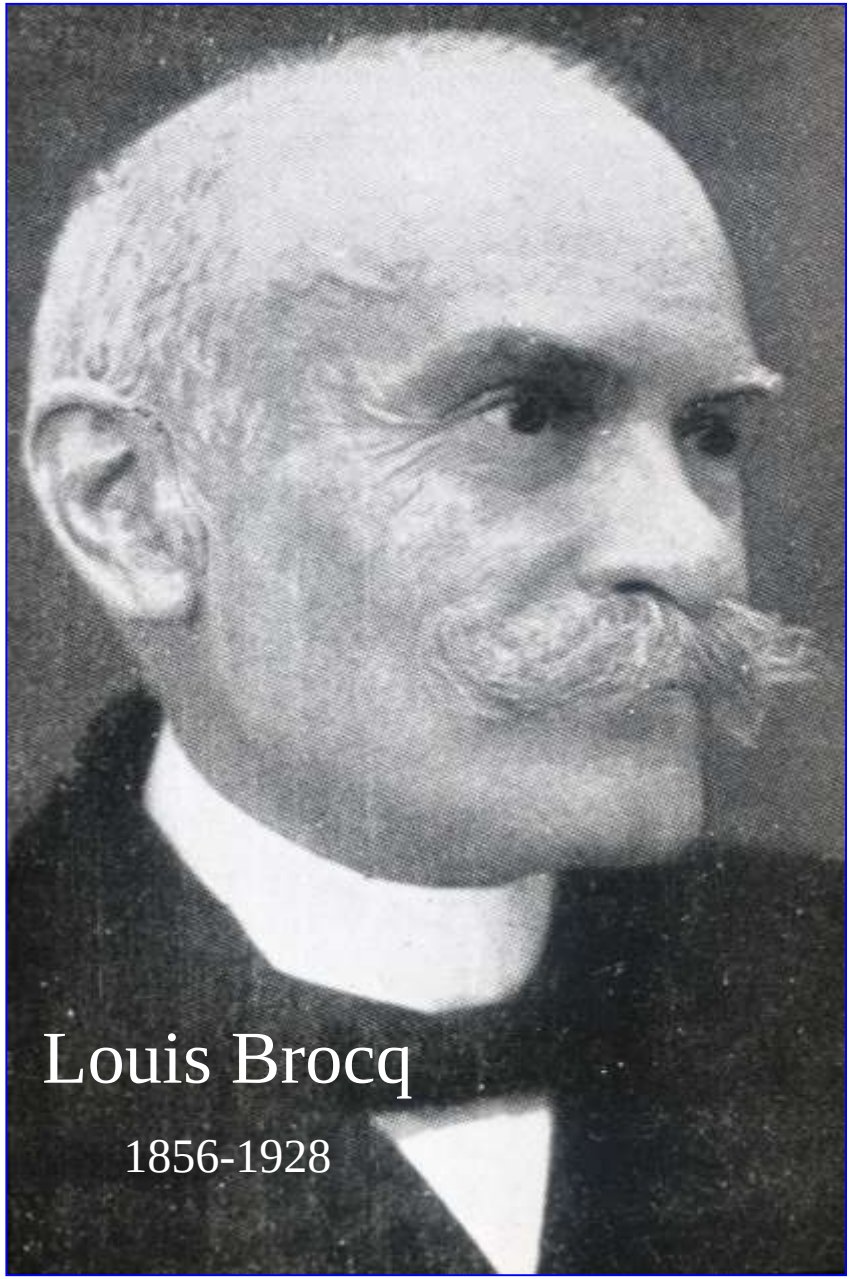
In an article about chilblain lupus, he expressed his concept of inflammatory skin diseases in these words:



Those who hold that such words as lupus, psoriasis, and acne are names for ‘clinical entities‘, which always keep close to their type, may find such cases as these very difficult to classify. For myself, having long held and taught that these names only apply to certain peculiar forms of inflammation of the skin due to causes and inherited proclivities which may easily be intermixed, I feel no hesitation in assigning them to a numerous and varied class of hybrids.

Jonathan Hutchinson, 1896

“Those who hold that such words as lupus, psoriasis, and acne are names for ‘clinical entities,’ which always keep close to their type, may find such cases as these very difficult to classify. For myself, having long held and taught that these names only apply to certain peculiar forms of inflammation of the skin due to causes and inherited proclivities which may easily be intermixed, I feel no hesitation in assigning them to a numerous and varied class of hybrids.”



LA THÉORIE DES FAITS DE PASSAGE

Quand on étudie avec soin les divers types morbides cutanés, on s'aperçoit qu'entre chacun d'eux et les types morbides voisins il existe une série complète de faits de passage établissant entre eux d'intimes traits d'union.

Cette importante particularité est connue depuis longtemps, et nous n'avons certes pas la prétention de l'avoir découverte : elle a été signalée par quelques observateurs, mais d'une façon toute incidente ; et, jusqu'en 1893, elle n'a pas frappé l'attention des médecins. Ce fut à cette époque qu'ayant depuis quelques années déjà remarqué la fréquence des faits de passage qui existent entre les divers groupes morbides que nous avions longuement étudiés, comme les éruptions généralisées rouges, les éruptions bulleuses, les lichens, les psoriasis, les eczémas, et ce que l'on appelait alors les eczémas séborrhéiques, nous eûmes l'idée de faire un travail d'ensemble sur cette question.

TRAVAUX ORIGINAUX

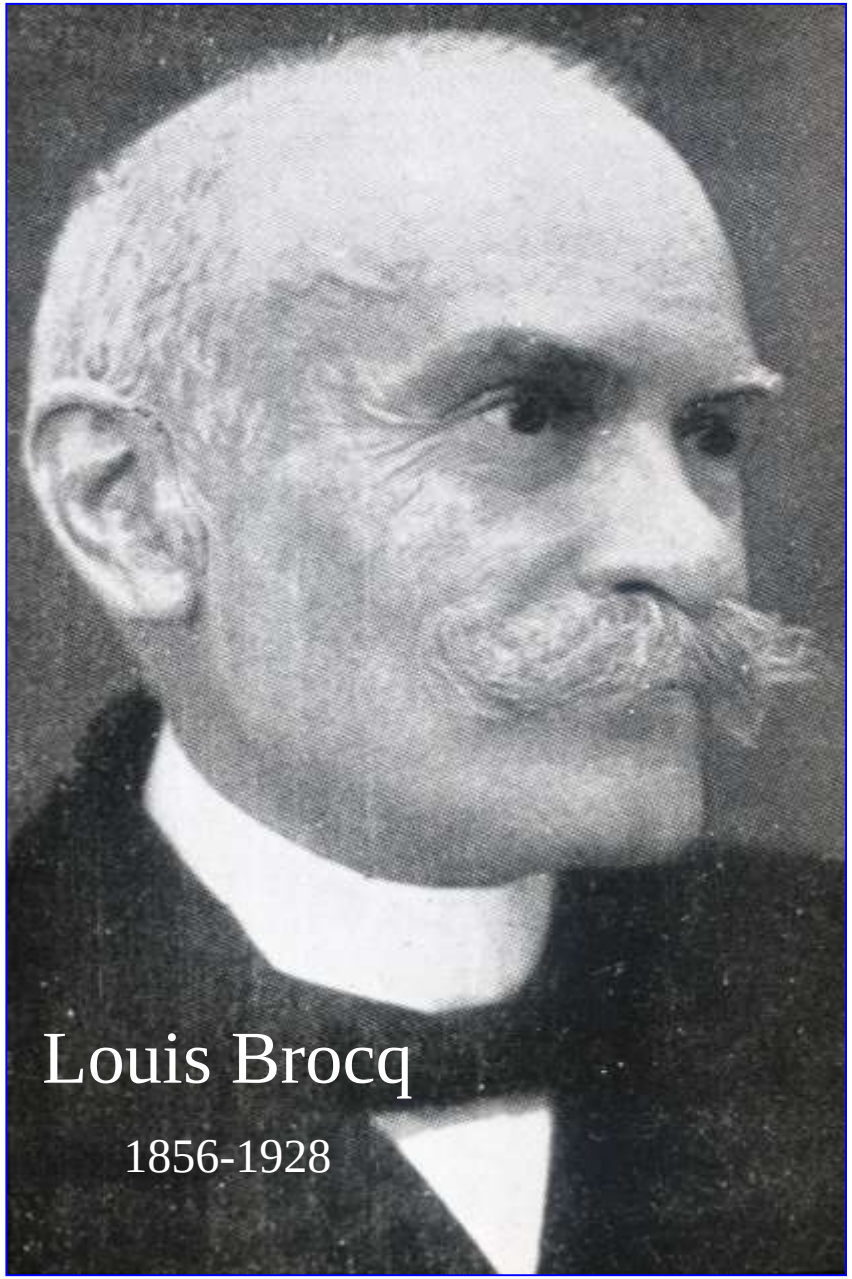
LES PARAPSORIASIS

Par **L. Brocq.**

Depuis quelques années, il paraît de temps en temps des travaux sur des dermatoses relativement assez rares, caractérisées essentiellement par de la rougeur du derme et par de la desquamation sèche plus ou moins marquée : les éléments sont plus ou moins étendus ; dans certains cas, ils ont à peine les dimensions d'une tête d'épingle, d'une lentille, dans d'autres ils arrivent à avoir celles de la paume de la main et même davantage. Leur coloration est plus ou moins accentuée. Mais, règle générale, ils ont, en outre, les caractères communs suivants : 1° peu ou point d'infiltration des téguments ; 2° peu ou point de prurit ; 3° évolution des plus lentes ; 4° peu de tendance à la guérison.

Ce groupe de dermatoses est évidemment très voisin du psoriasis : les malades qui en sont atteints sont même presque toujours considérés comme ayant une variété avortée ou anomale de psoriasis. Cependant certaines formes ressemblent assez au lichen planus, d'autres aux séborrhéides pityriasiques ou psoriasiformes, d'où les noms divers qui ont été donnés à ces affections.

Likewise, French dermatologist Louis Brocq thought of diseases as reaction patterns of the body that had no firm boundaries and could eventuate into each other, a concept to which he referred as *“théorie de faits de passage.”* In his famous article on parapsoriasis in 1902, he noted:



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We believe that there are no gaps nosologically in the chain of morbid findings or true pathologic entities. In botany and zoology, there are no empty spaces in the sequence of organisms. When there is a gap today, it has not existed before, and one finds in paleontology the traces of extinguished species. In the same way, every pathologic condition ... is connected with neighboring affections by a series of transitional steps.

Louis Brocq, 1902

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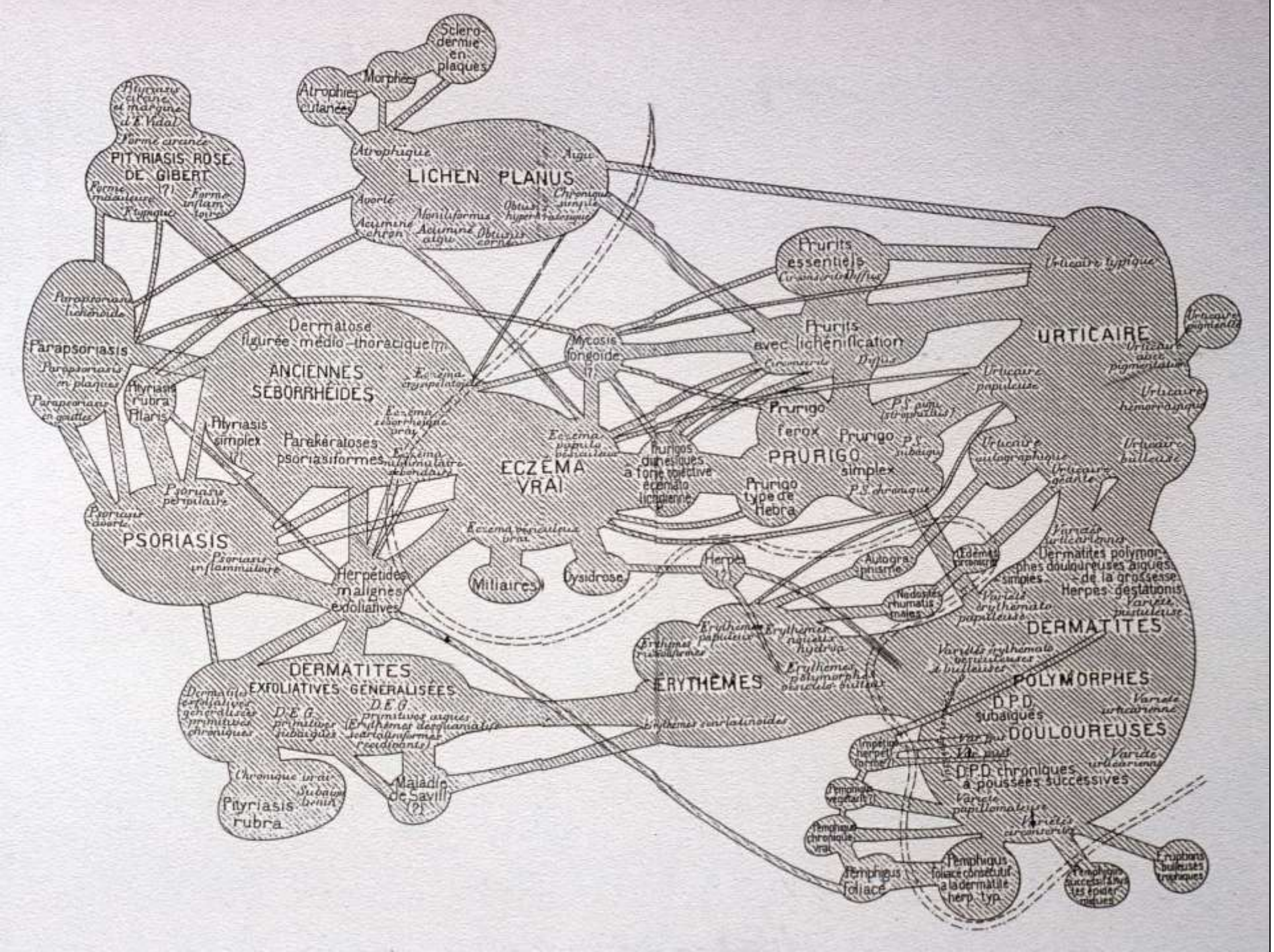
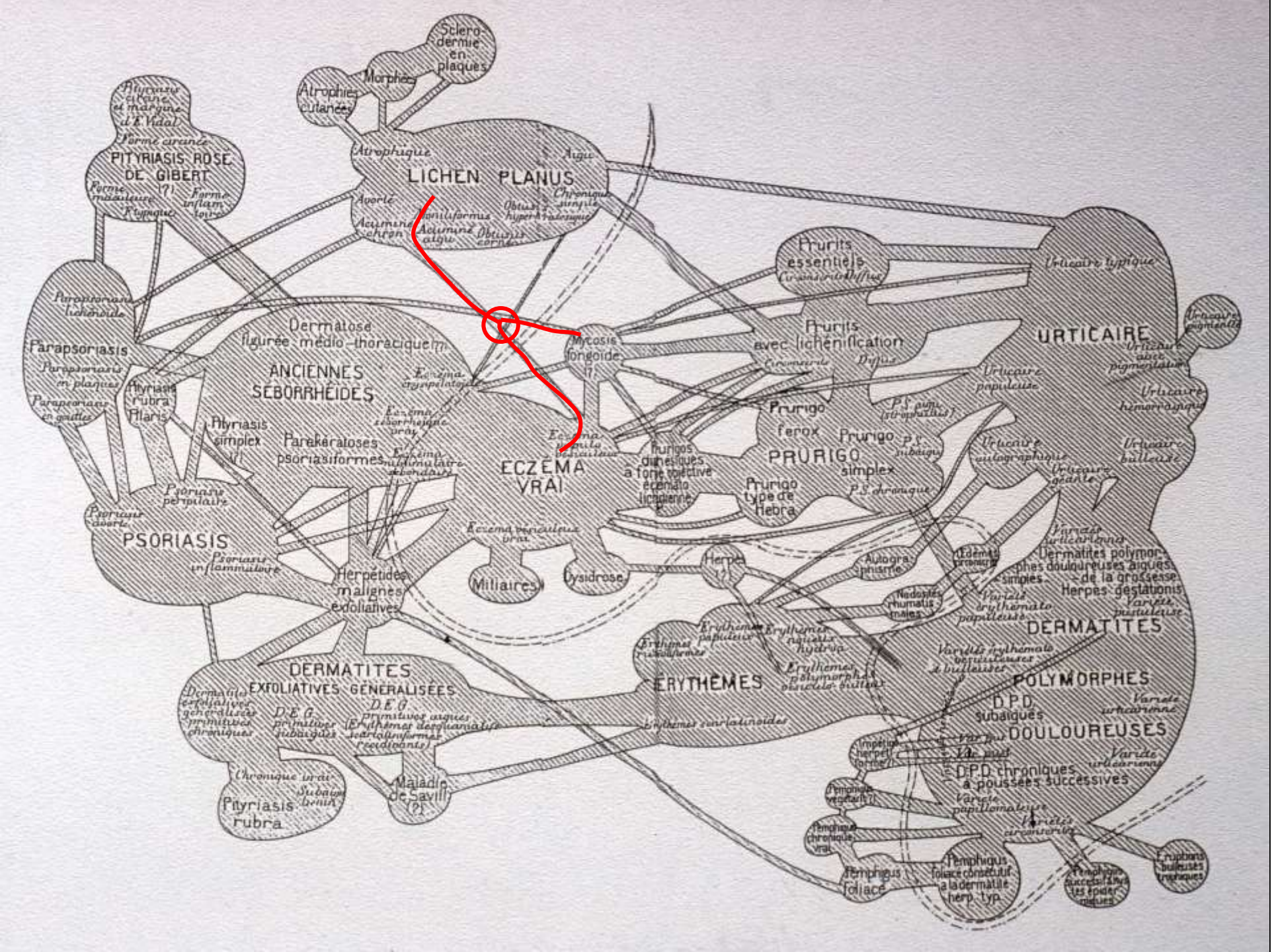


Brocq illustrated his concept graphically by connecting skin diseases through lines and columns of different thickness that were said to reflect the degree of relationship of reaction patterns to one another. He referred to those graphs as the “nebulas of dermatoses” and claimed



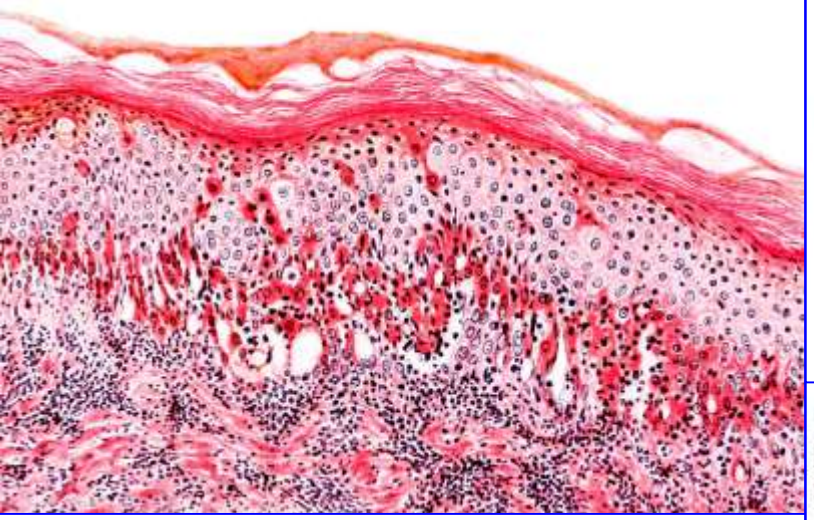
that a given patient could attain any position and thus suffer, for example, from a mixture of eczema, mycosis fungoides, and lichen planus. The diagnostic effort consisted of determining the precise position of a patient among the “nebulas” that allegedly reflected the relative importance of each pattern in the individual case. In his article on the different types of parapsoriasis

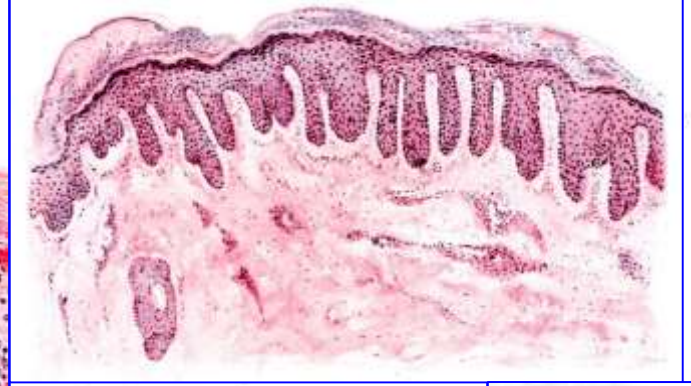
Rien de plus simple … que de classifier par cette méthode les divers faits cliniques un peu ambigus ou mixtes ...

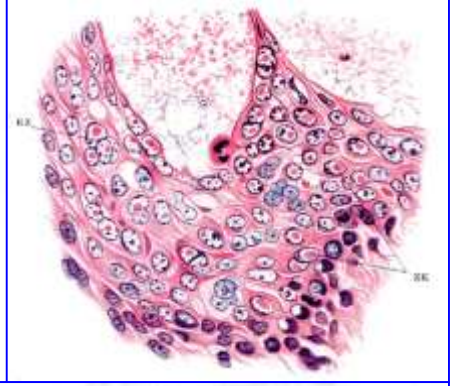
Louis Brocq, 1902

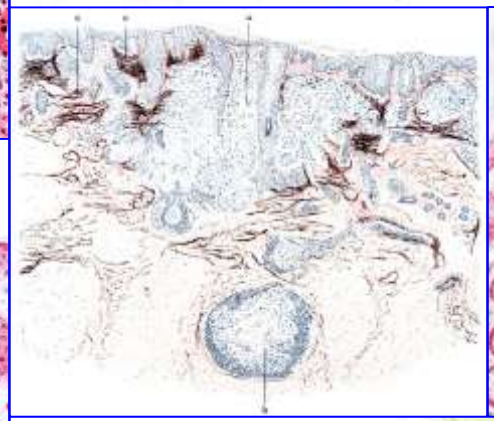
Brocq concluded triumphantly: *"Nothing is easier than to classify by this method the various ambiguous or mixed clinical cases."* And he was right. His "graphical method" offered a solution for any diagnostic problem, but it did not reflect reality because it paid no heed to the specificity of pathologic processes; its easy solutions were illusions that did not provide a basis for the rational management of patients.

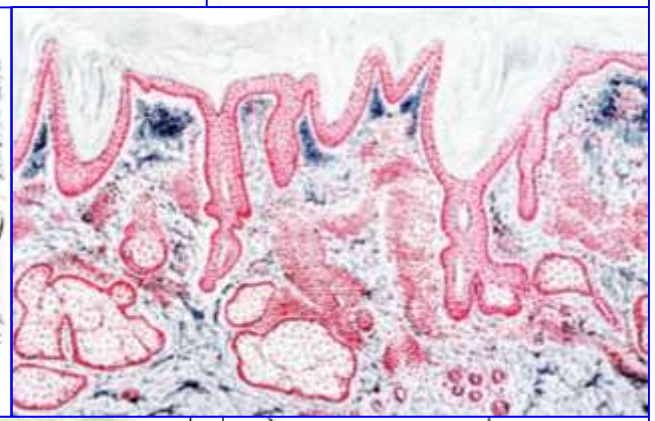
Brocq's nebulous concepts may be explained, in part, by the fact that he was a clinician only.

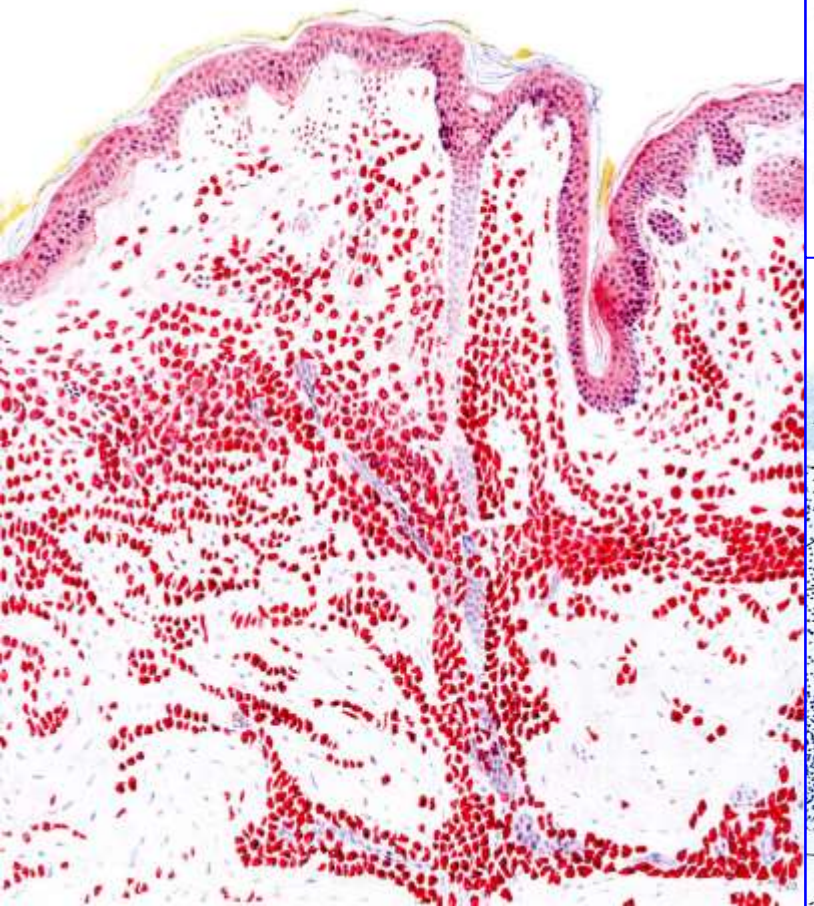


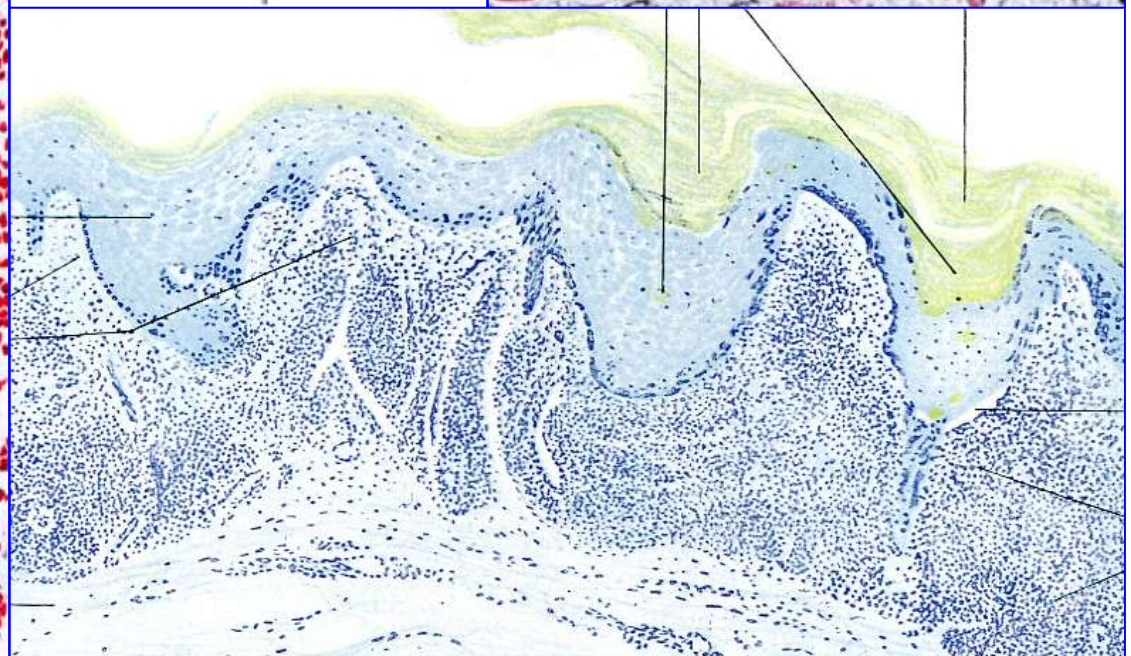




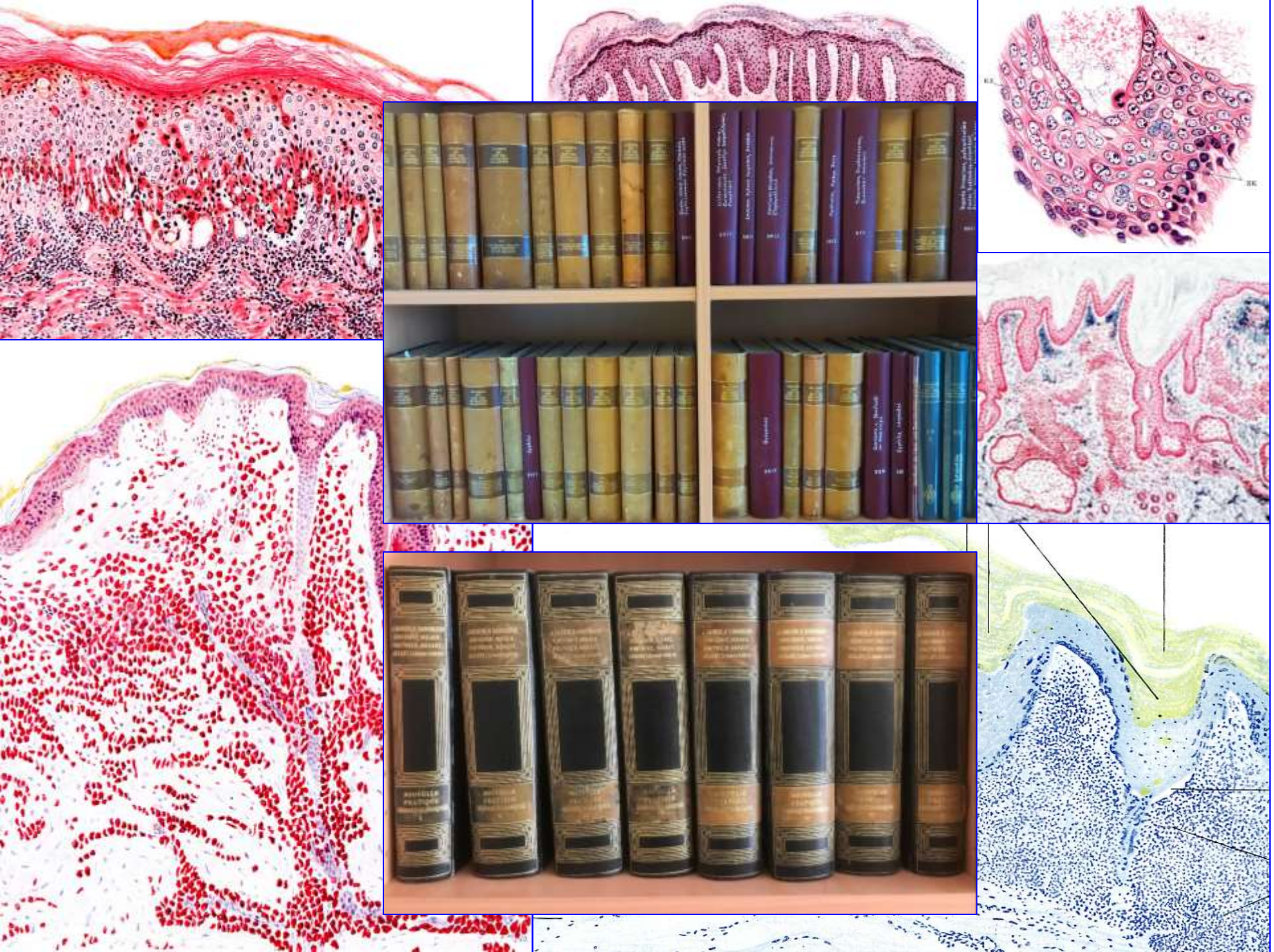




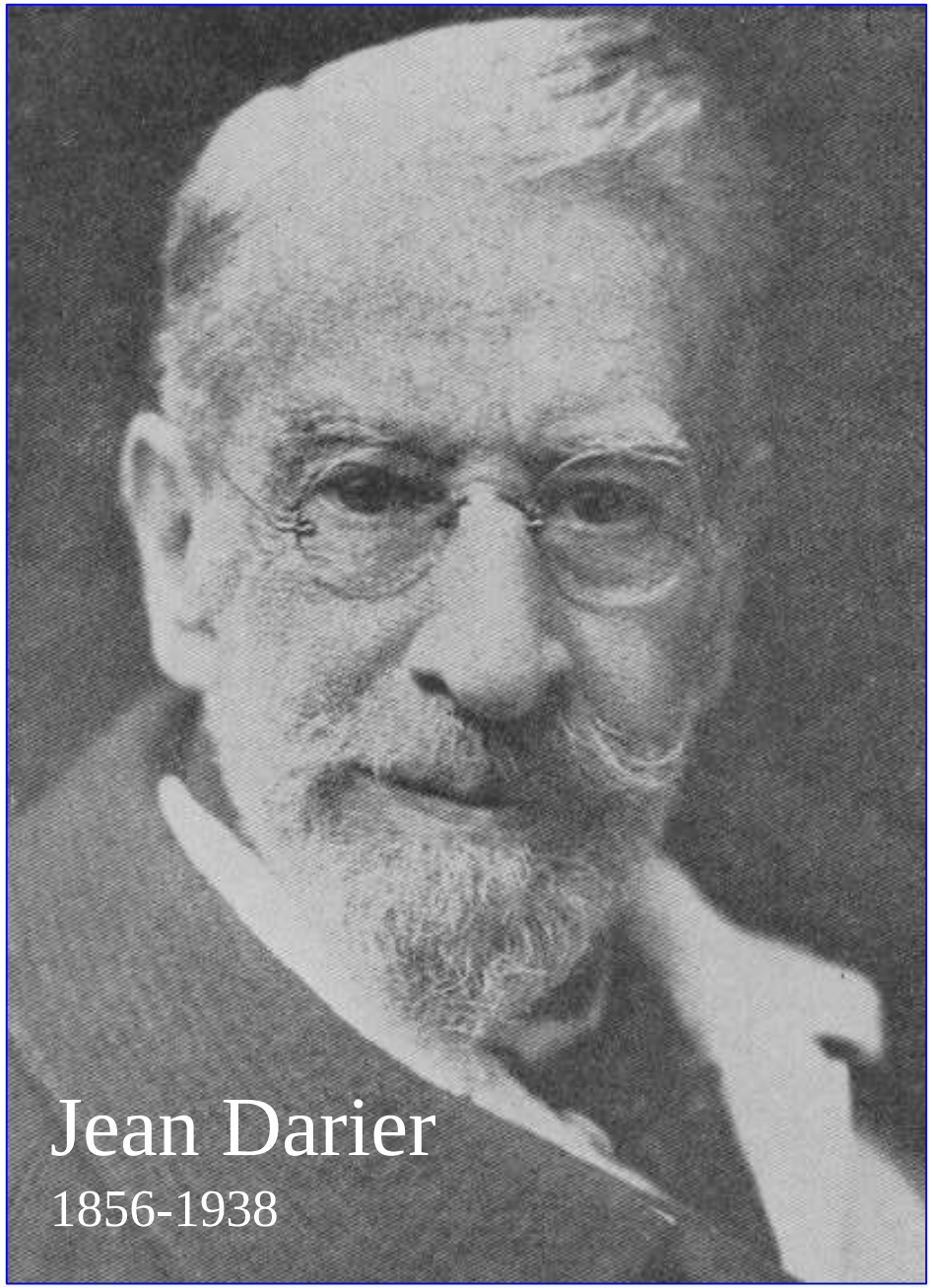


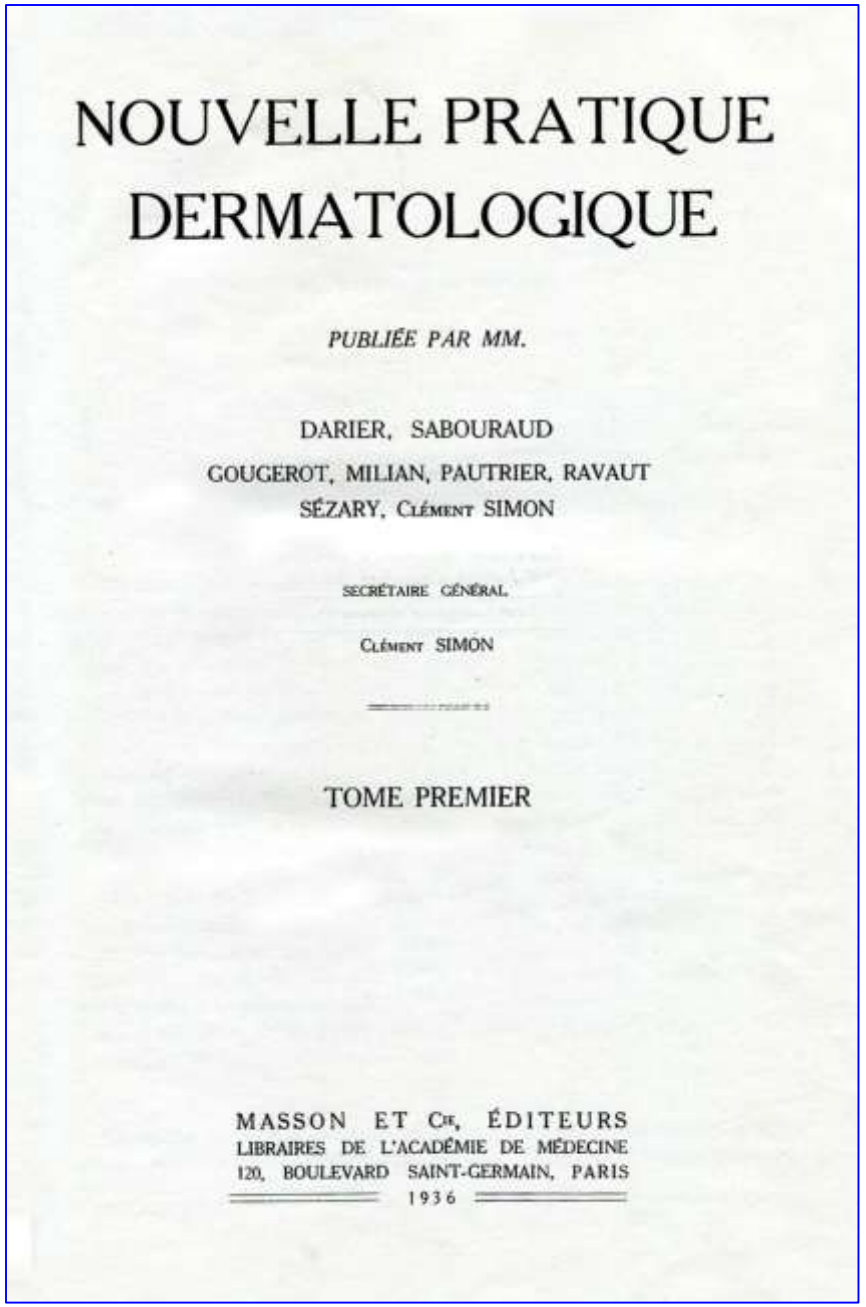


The next generation of dermatologists was also conversant with histopathology, and as diseases were assessed more completely,



and described comprehensively in the multi-volume textbooks of the 1930s, such as those by Jadassohn and Darier, their distinct nature was appreciated.





NOUVELLE PRATIQUE DERMATOLOGIQUE

PUBLIÉE PAR MM.

DARIER, SABOURAUD
GOUGEROT, MILIAN, PAUTRIER, RAVAUT
SÉZARY, CLÉMENT SIMON

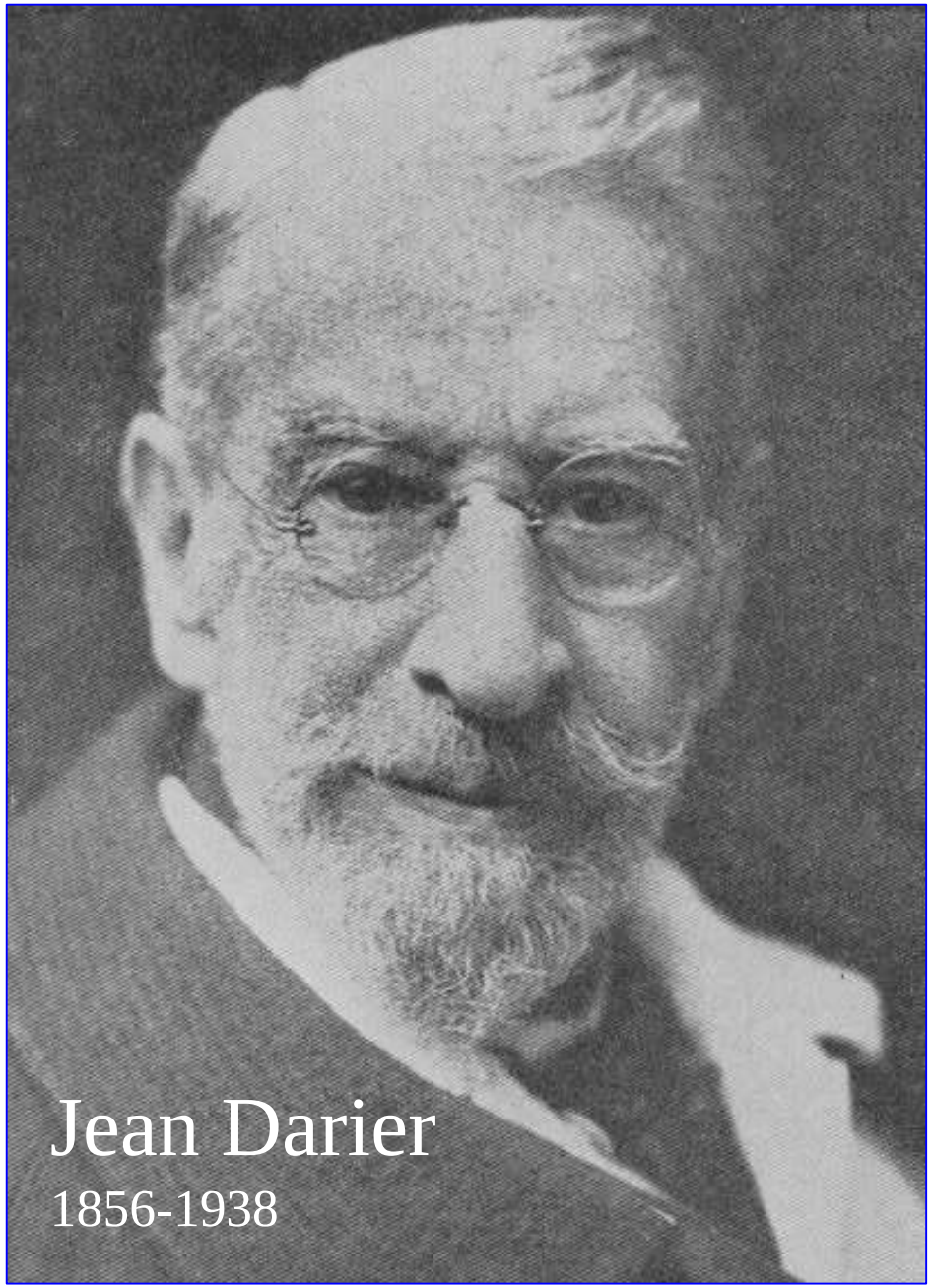
SECRÉTAIRE GÉNÉRAL

CLÉMENT SIMON

TOME PREMIER

MASSON ET CIE, ÉDITEURS
LIBRAIRES DE L'ACADÉMIE DE MÉDECINE
120, BOULEVARD SAINT-GERMAIN, PARIS
1936

When Jean Darier, a former co-worker of Brocq and pioneer of dermatohistopathology, discussed the “théorie de faits de passage” in 1936,



Jean Darier
1856-1938

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lésions, de conditions étiologiques et de processus pathogéniques parfois remarquablement complexes. Les cas cliniques où ces combinaisons interviennent sont si peu exceptionnels, qu'ils sont pour ainsi dire le pain quotidien du clinicien.

Nous venons de dire que son rôle est d'analyser et de peser ce que la nature a entremêlé. S'il a entendu parler des ***faits de passage***, auxquels nous avons fait allusion au début de ce paragraphe, il est à craindre qu'il ne se laisse tenter par le piège qui l'inviterait à accepter une interprétation commode, et n'exigeant pas d'efforts.

La formule « ***faits de passage*** » ou « ***de transition*** » ayant été introduite par des cliniciens de premier ordre, nous croyons devoir en préciser le contenu.

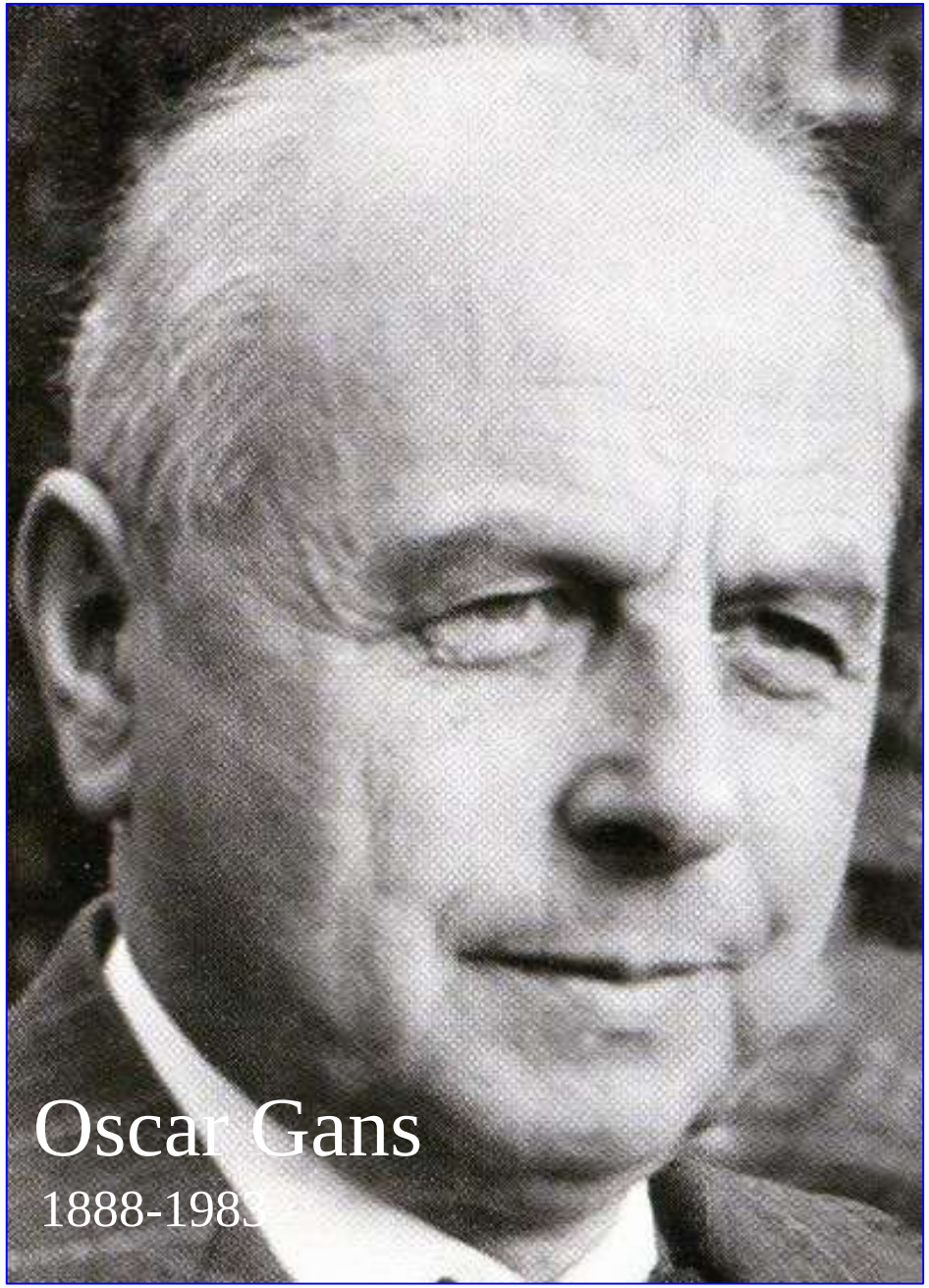
D'incontestables faits de passage se rencontrent entre les formes cliniques d'un même processus morbide, selon ses stades, ses degrés, ses localisations. Il existe des faits de passage entre les diverses formes de la tuberculose cutanée, allant de l'ulcère tuberculeux le plus typique jusqu'à certaines tuberculides.

Mais il ne saurait exister de faits de passage entre la tuberculose, la lèpre,

The content of the formula … which has been introduced by clinicians of first order should be specified. Incontestable faits de passage are encountered among clinical forms of the same pathologic process, depending on stages, degrees, and localizations. … But there cannot exist faits de passage between tuberculosis, leprosy, syphilis, etc.; the coexistence of two distinct specific processes is a complication, not a transition.

Jean Darier, 1936

he cautioned that *"the content of the formula … which has been introduced by clinicians of first order should be specified. Incontestable faits de passage are encountered among clinical forms of the same pathologic process, depending on stages, degrees, and localizations. … But there cannot exist faits de passage between tuberculosis, leprosy, syphilis, etc.; the coexistence of two distinct specific processes is a complication, not a transition."*



HISTOLOGIE
DER HAUTKRANKHEITEN

DIE GEWEBSVERÄNDERUNGEN
IN DER KRANKEN HAUT UNTER BERÜCKSICHTIGUNG
IHRER ENTSTEHUNG UND IHRES ABLAUFS

VON

DR. MED., DR. MED. OSCAR GANS
ORD. PROFESSOR DER DERMATOLOGIE,
DIREKTOR DER KLINIK UND POLIKLINIK FÜR HAUT- UND GESCHLECHTSKRANKHEITEN
AN DER UNIVERSITÄT FRANKFURT A. MAIN

UND

DR. MED. GERD-KLAUS STEIGLEDER
PRIVATDOZENT DER DERMATOLOGIE,
OBERARZT DER UNIVERSITÄTS-HAUTKLINIK FRANKFURT A. MAIN

ERSTER BAND

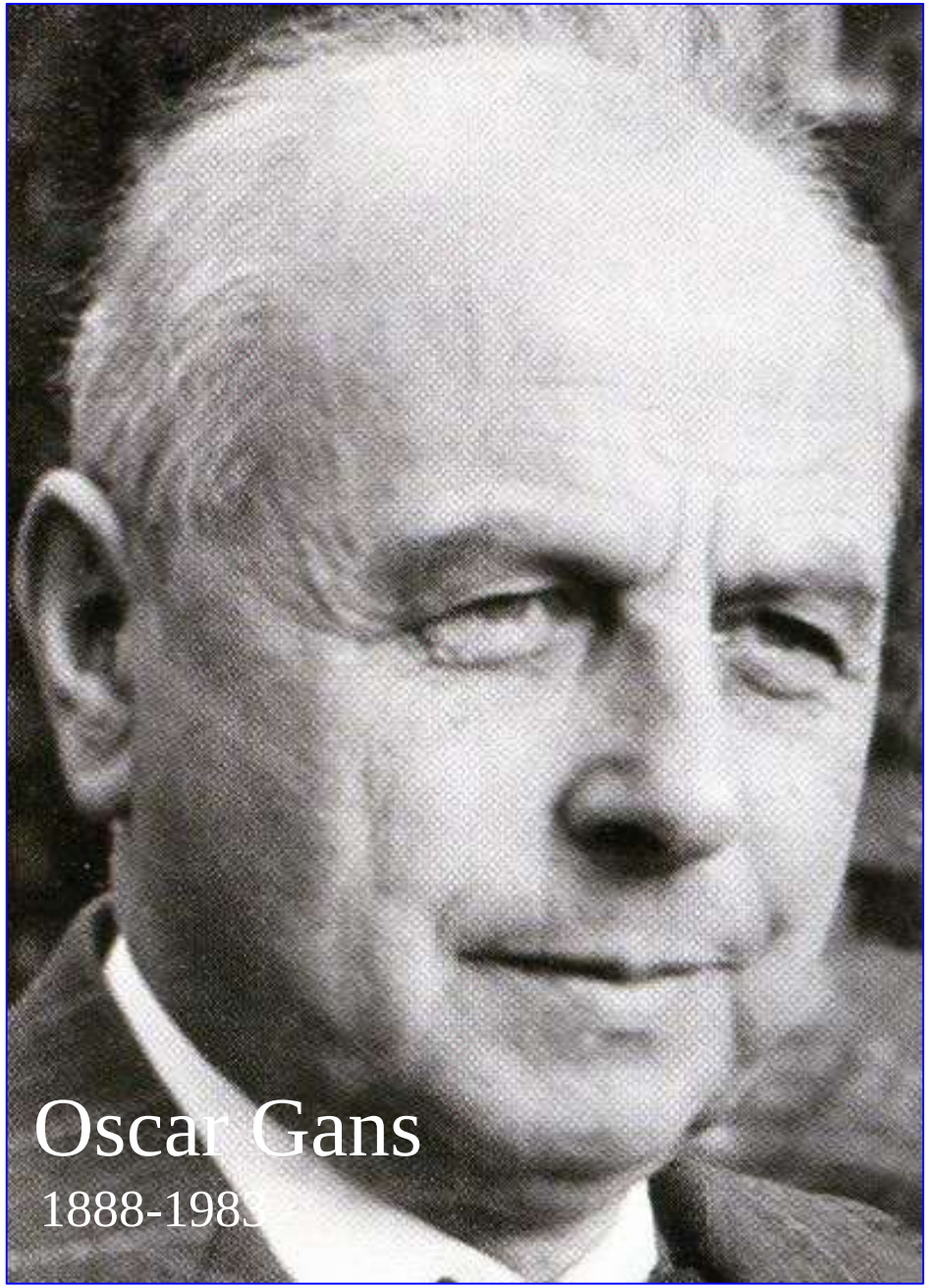
NORMALE ANATOMIE
UND ENTWICKLUNGSGESCHICHTE
LEICHENERSCHEINUNGEN
DERMATOPATHIEN · DERMATITIDEN I

MIT 258 MEIST FARBIGEN ABBILDUNGEN

ZWEITE AUFLAGE

SPRINGER-VERLAG
BERLIN · GÖTTINGEN · HEIDELBERG
1955

With the specificity of diseases being recognized, and more and more findings being described, diagnosis did not become easier. In the second edition of his textbook “Histology of Skin Diseases” in 1955, Oscar Gans complained



HISTOLOGIE
DER HAUTKRANKHEITEN

DIE GEWEBSVERÄNDERUNGEN
IN DER KRANKEN HAUT UNTER BERÜCKSICHTIGUNG
IHRER ENTSTEHUNG UND IHRES ABLAUFS

VON

DR. MED., DR. MED. OSCAR GANS
ORD. PROFESSOR DER DERMATOLOGIE,
DIREKTOR DER KLINIK UND POLIKLINIK FÜR HAUT- UND GESCHLECHTSKRANKHEITEN
AN DER UNIVERSITÄT FRANKFURT A. MAIN

UND

DR. MED. GERD-KLAUS STEIGLEDER
PRIVATDOZENT DER DERMATOLOGIE,
OBERARZT DER UNIVERSITÄTS-HAUTKLINIK FRANKFURT A. MAIN

Although we now know much more details and this increase in knowledge has made the field more colourful, the subject did not become more understandable ... As our knowledge has increased, analysis of differential diagnosis has become considerably more difficult.

Oscar Gans, 1955

that *"although we now know much more details and this increase in knowledge has made the field more colourful, the subject did not become more understandable ... As our knowledge has increased, analysis of differential diagnosis has become considerably more difficult."*

In brief, diseases were defined better, but they were not easy to identify. An identification scheme was needed, and in that regard, progress was made especially in the field of dermatohistopathology.

A GUIDE TO DERMATOHISTOPATHOLOGY

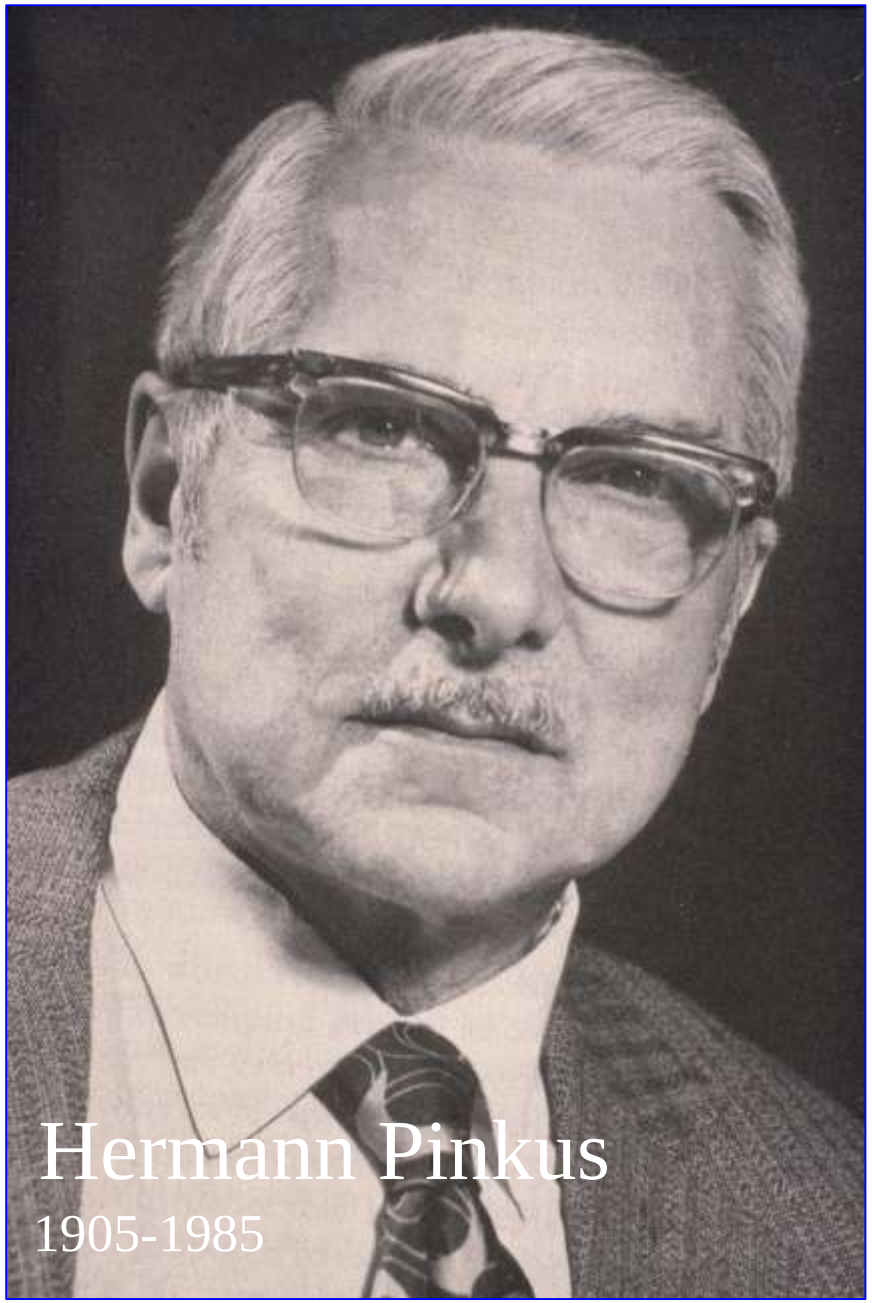
HERMANN PINKUS, M.D., M.S.

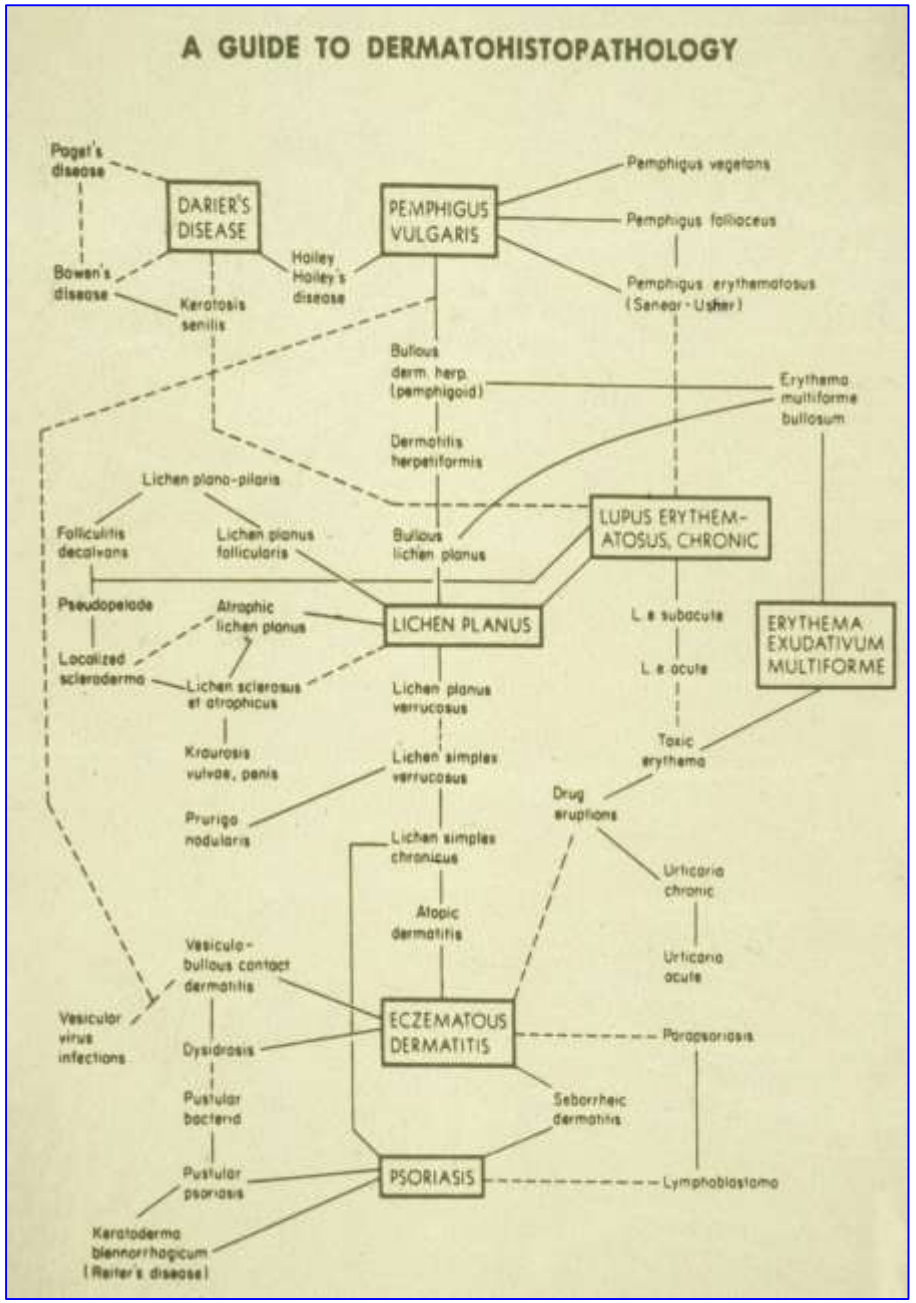
Professor and Chairman, Department of Dermatology and Syphilology, Associate, Department of Pathology, Wayne State University School of Medicine, Detroit, Michigan; Senior Attending Dermatologist, Detroit General Hospital; Chief, Dermatology Section, Veterans Administration Hospital, Allen Park, Michigan

AMIR H. MEHREGAN, M.D.

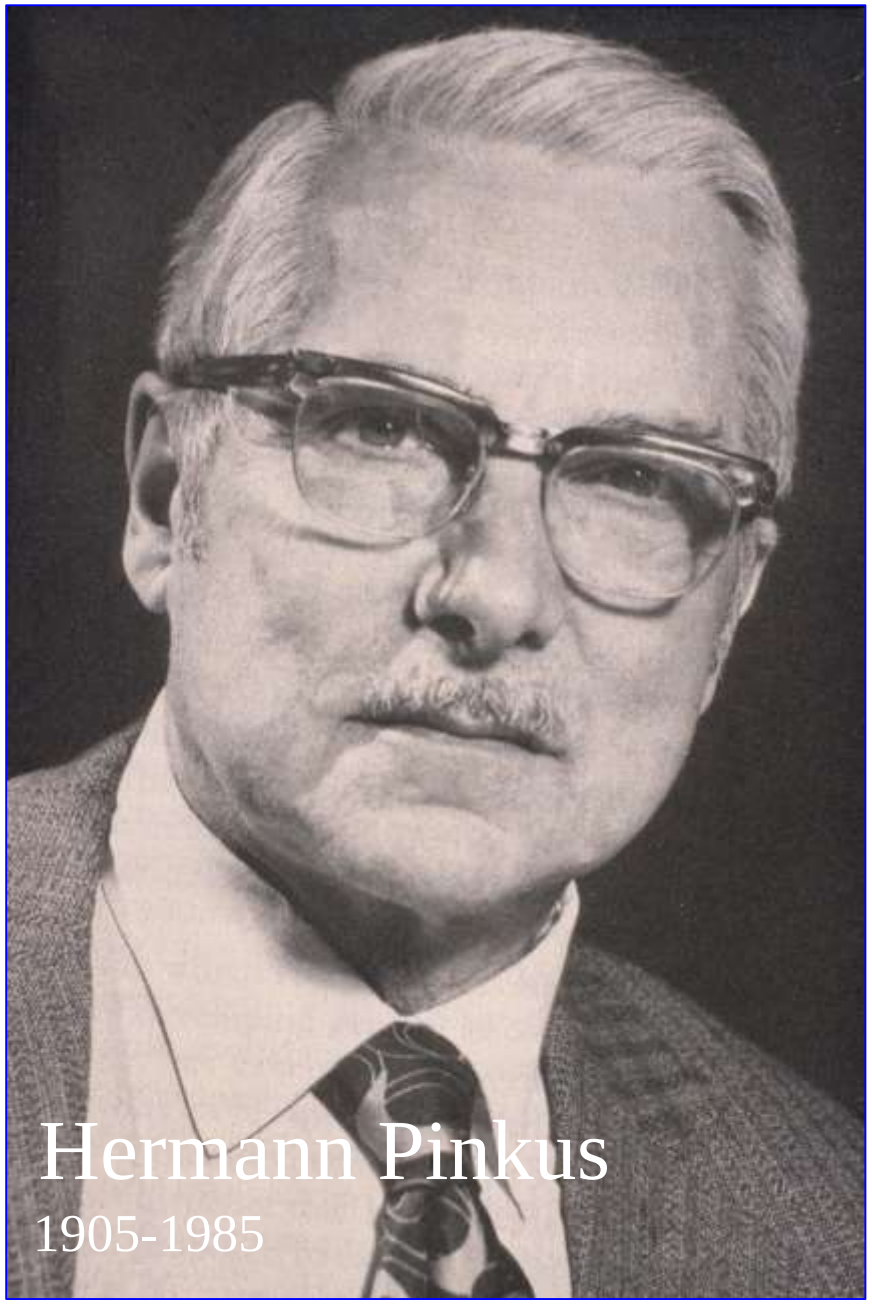
Adjunct Associate Professor, Department of Dermatology and Syphilology, Associate, Department of Pathology, Wayne State University School of Medicine, Detroit, Michigan; Senior Associate Dermatologist, Detroit General Hospital

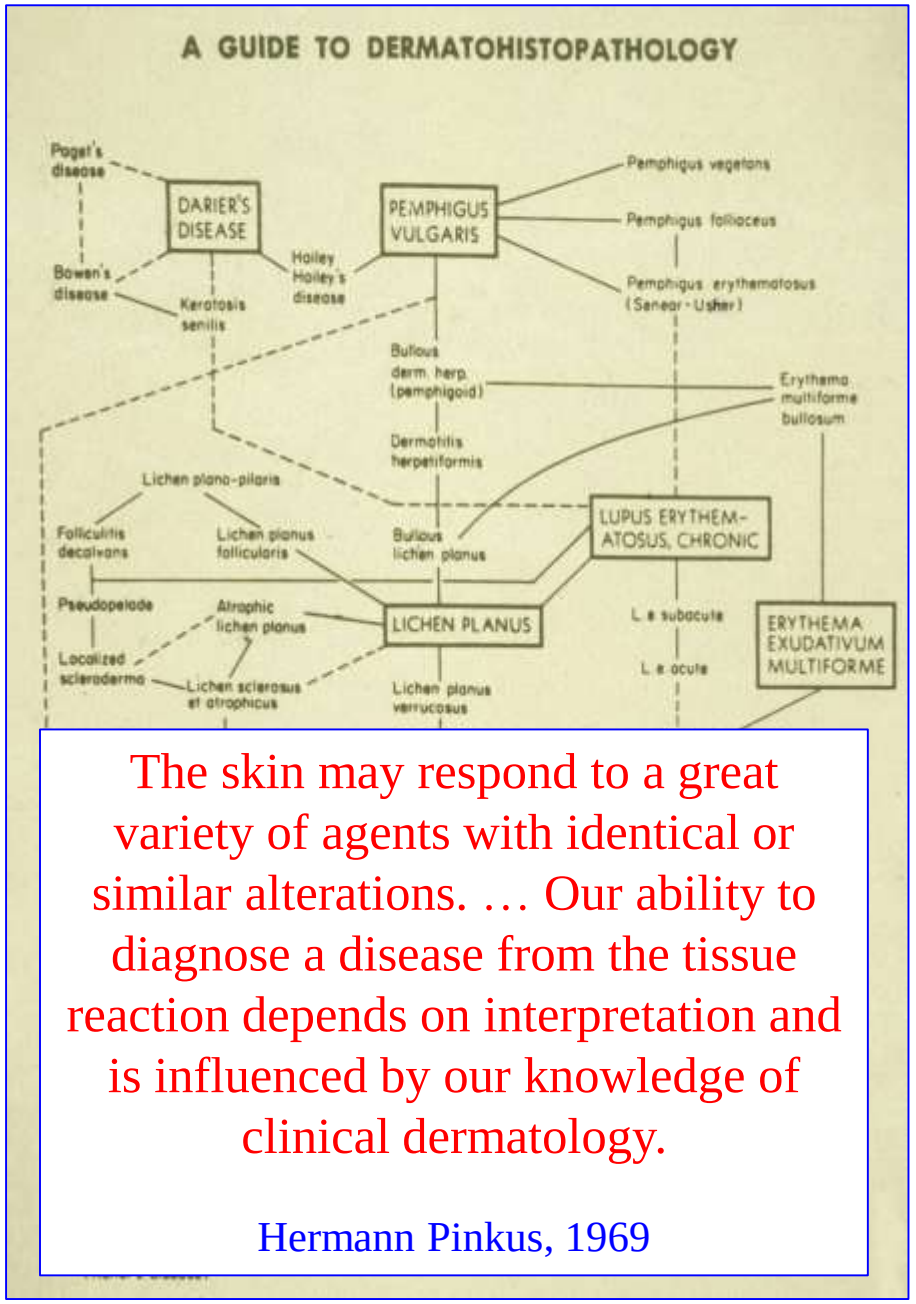
In 1969, Hermann Pinkus published his “Guide to Dermatohistopathology”



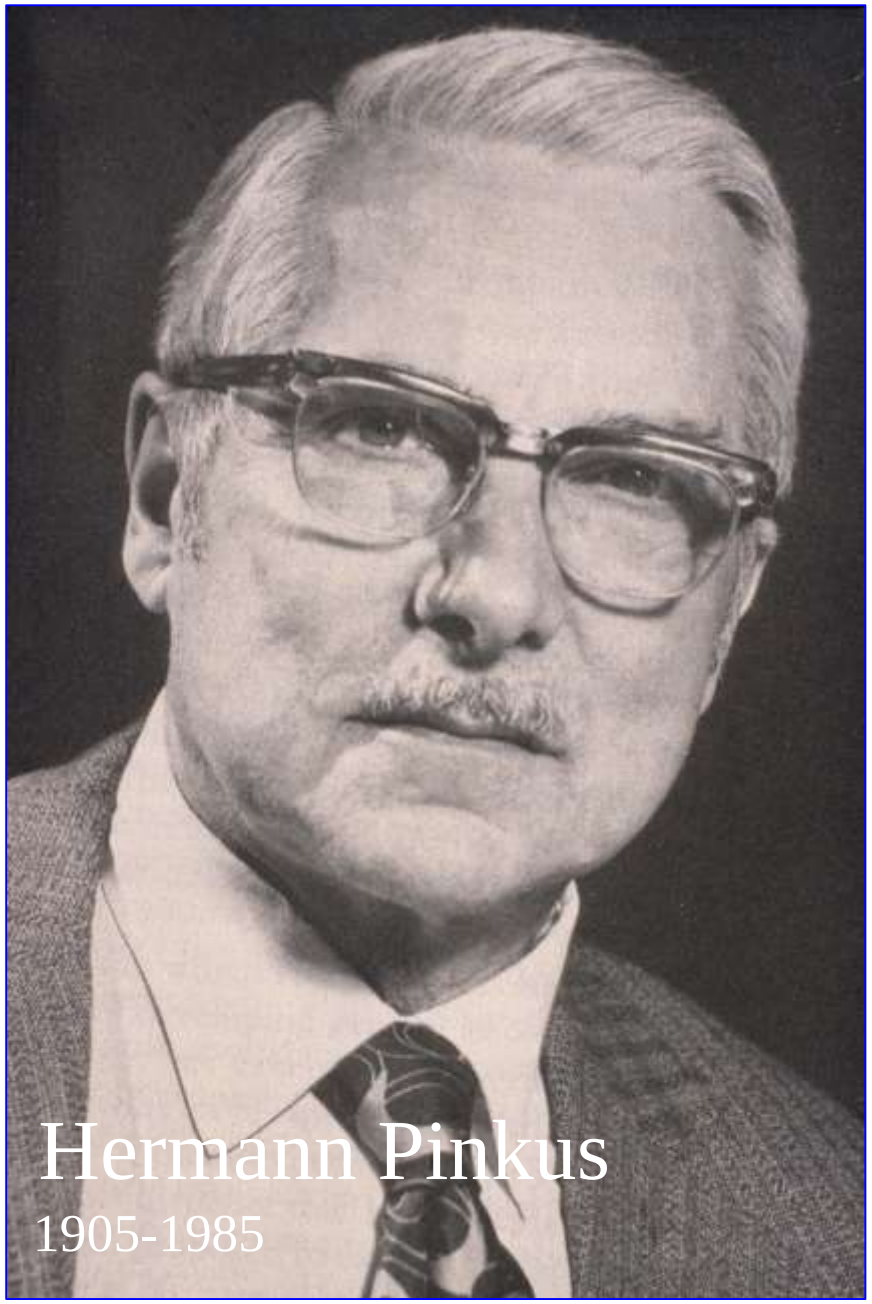


in which diseases were arranged according to histopathologic similarities.





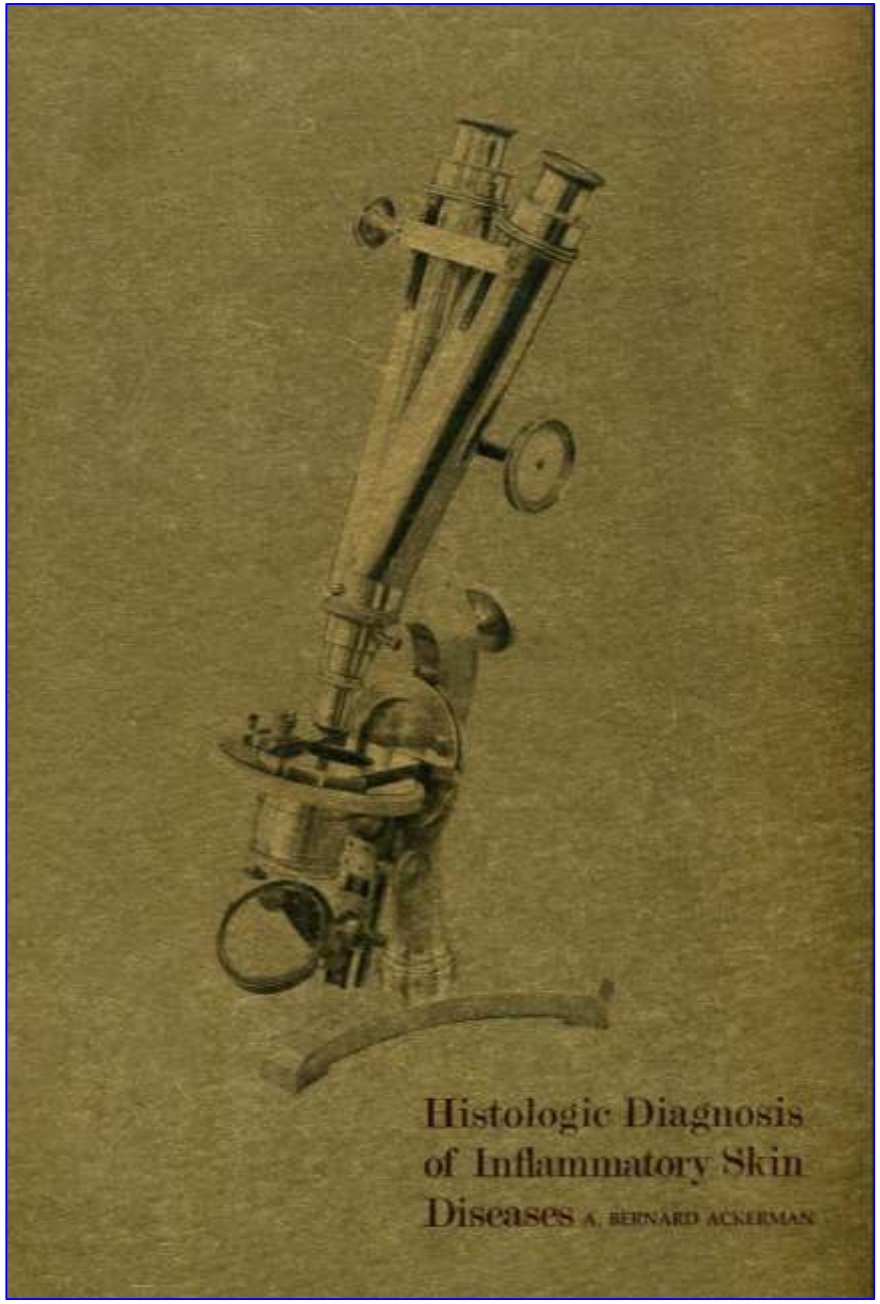
Pinkus pointed out that *"the skin may respond to a great variety of agents with identical or similar alterations. … Our ability to diagnose a disease from the tissue reaction depends on interpretation and is influenced by our knowledge of clinical dermatology."*



Hermann Pinkus
1905-1985

II / Superficial Inflammatory Processes

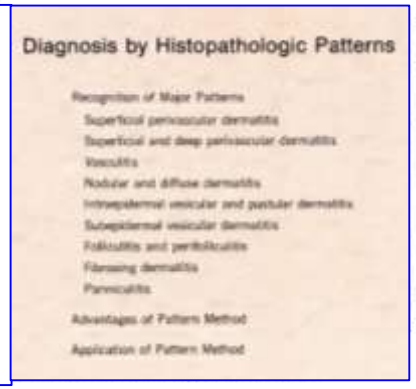
Pinkus described several stereotypic reaction patterns but made a clear distinction between the non-specific pattern and the specific disease.



The method by pattern analysis was elaborated on by A. Bernard Ackerman who, in his landmark textbook of 1978, “Histologic Diagnosis of Inflammatory Skin Diseases,”

Nine Strikingly Different Major Patterns

A.B. Ackerman, 1978



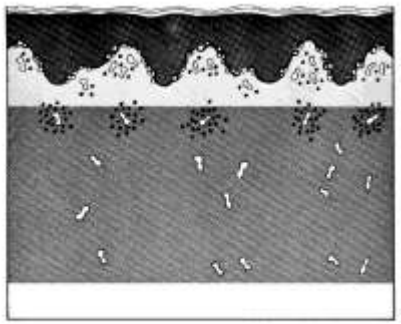


FIG. 6-3. A, Interface dermatitis with vacuolar alteration.

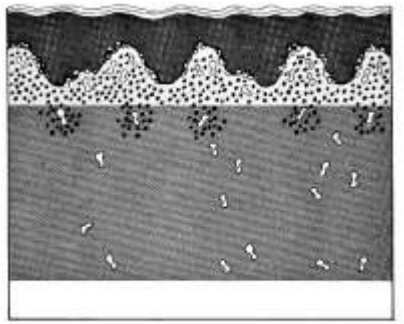


FIG. 6-3. B, Interface dermatitis with lichenoid infiltrate.

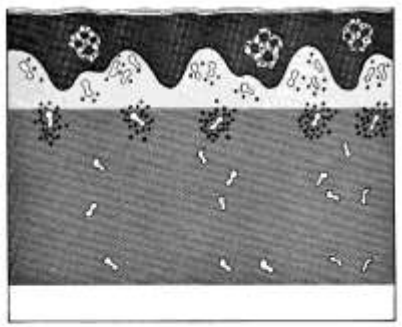


FIG. 6-4. Spongiotic dermatitis.

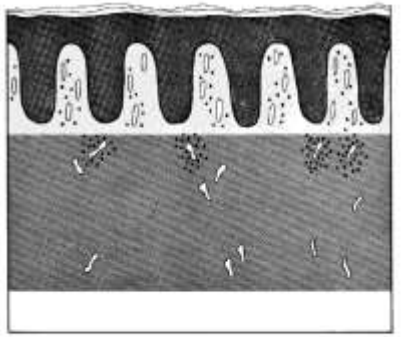


FIG. 6-5. Psoriasiform dermatitis.

170 HISTOLOGIC DIAGNOSIS OF INFLAMMATORY SKIN DISEASES

presented a consistent classification of diseases according to a single aspect, their histopathologic presentation. Skin diseases were classified by *"nine strikingly different major patterns"* assumed by infiltrates of inflammatory cells, and though Ackerman acknowledged that *"making definite diagnoses is not always possible,"*

By using the pattern method … the non-specific can become specific, and the apparently meaningless can become meaningful.

A.B. Ackerman, 1978

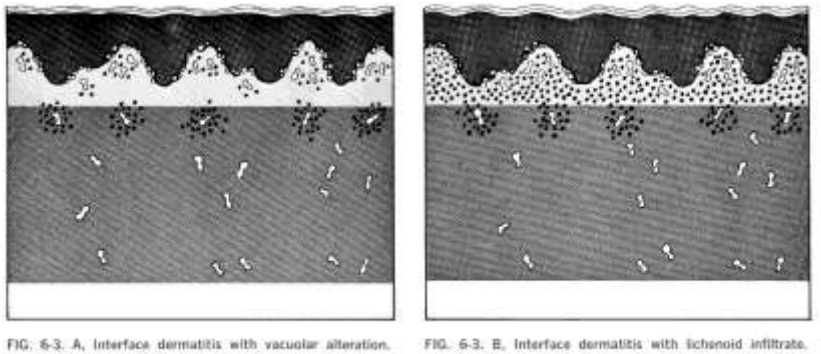
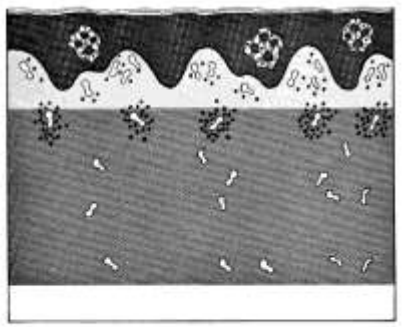


FIG. 6-3. A, Interface dermatitis with vacuolar alteration.

FIG. 6-3. B, Interface dermatitis with lichenoid infiltrate.



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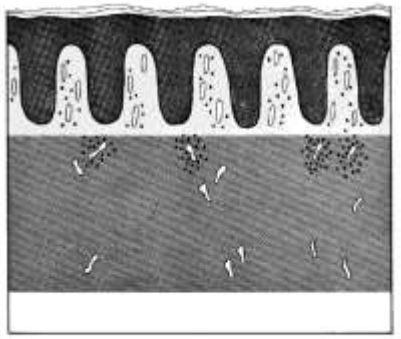
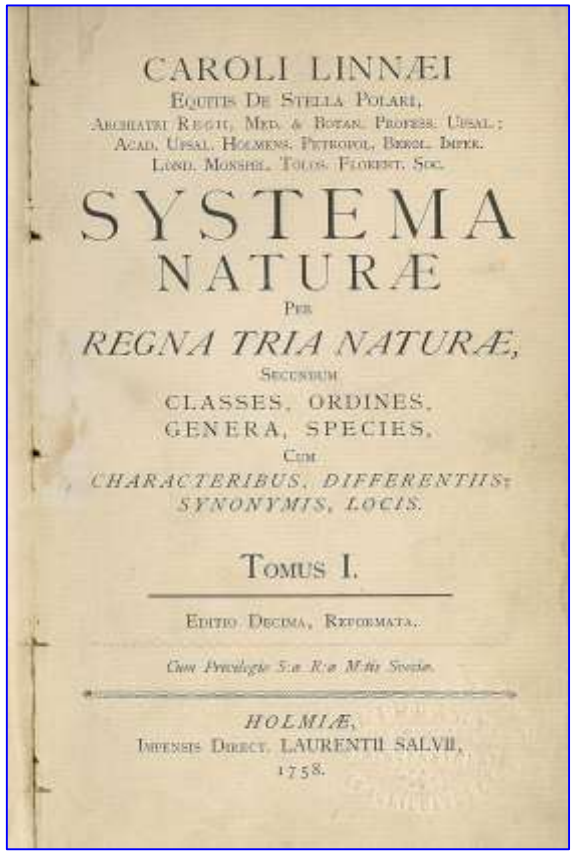


FIG. 6-5. Psoriasiform dermatitis.

170 HISTOLOGIC DIAGNOSIS OF INFLAMMATORY SKIN DISEASES

he insisted that, *"by using the pattern method … the non-specific can become specific, and the apparently meaningless can become meaningful."*


CAROLI LINNÆI
EQUITIS DE STELLA POLARI,
ARCHIATRI REGII, MED. & BOTAN. PROFESS. UPSAL.;
ACAD. UPSAL. HOLMENS. PETROPOL. BEROL. IMPER.
LOND. MONSPEL. TOLOS. FLORENT. SOC.

SYSTEMA NATURÆ

PER

REGNA TRIA NATURÆ,

SECUNDUM

CLASSES, ORDINES,
GENERA, SPECIES,

CUM

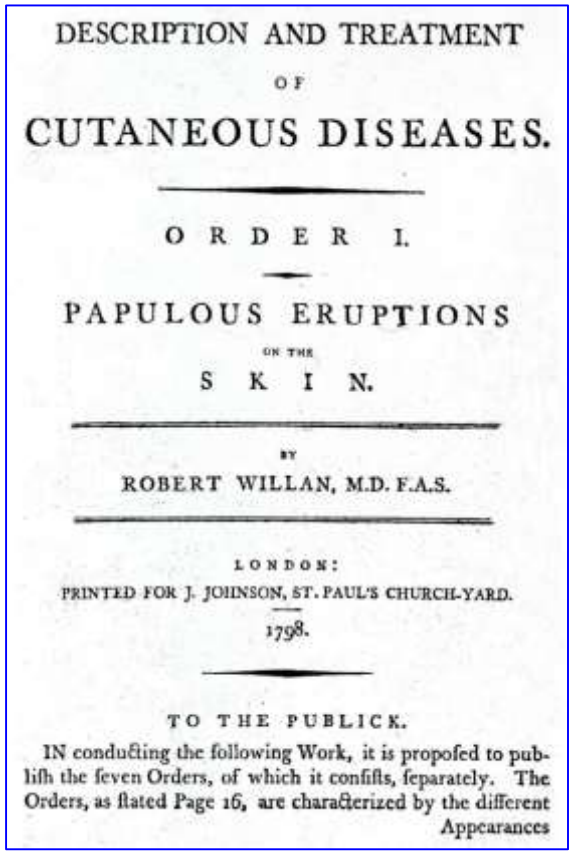
CHARACTERIBUS, DIFFERENTIIS,
SYNONYMIS, LOCIS.

TOMUS I.

EDITIO DECIMA, REFORMATA.

Cum Privilegio S.æ R.æ M.tis Sveciæ.

HOLMIÆ,
IMPENSIS DIRECT. LAURENTII SALVII,
1758.


DESCRIPTION AND TREATMENT
OF
CUTANEOUS DISEASES.

ORDER I.

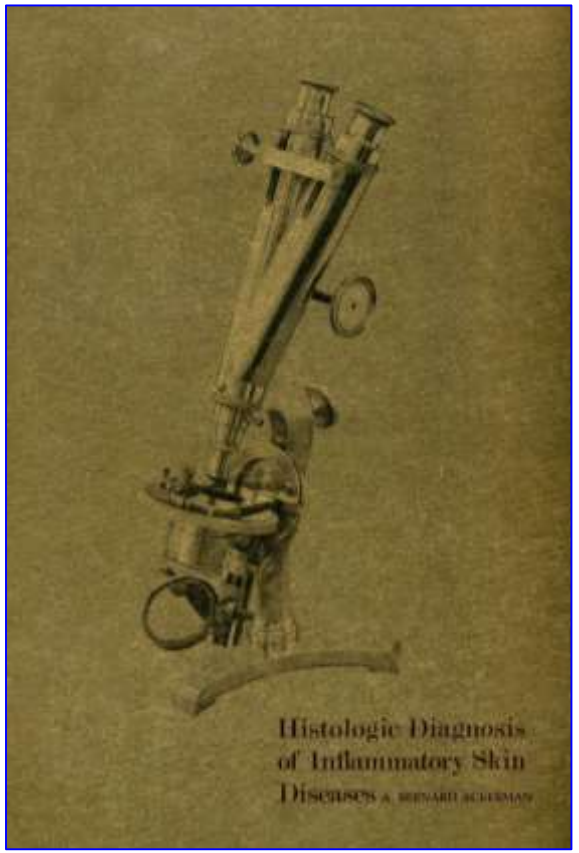
PAPULOUS ERUPTIONS
ON THE
SKIN.

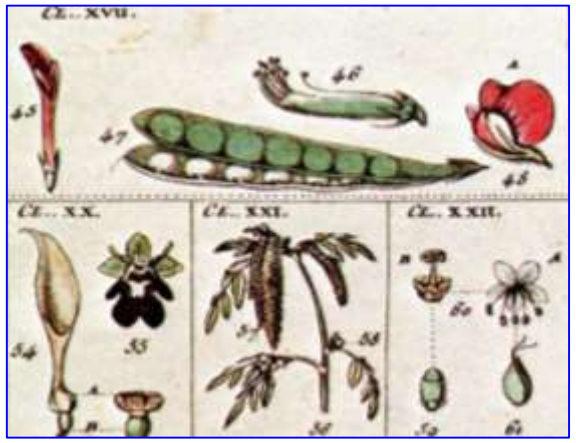
BY
ROBERT WILLAN, M.D. F.A.S.

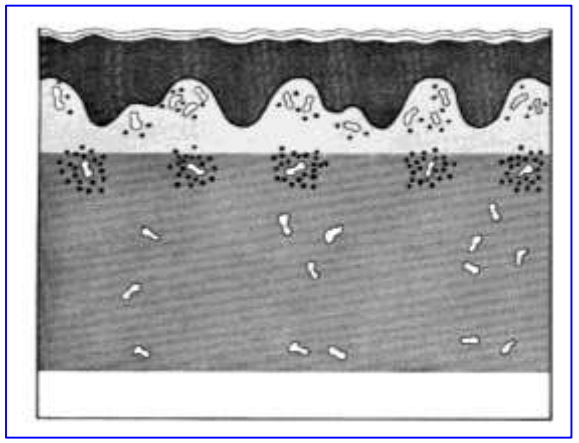
LONDON:
PRINTED FOR J. JOHNSON, ST. PAUL'S CHURCH-YARD.
1798.

TO THE PUBLICK.

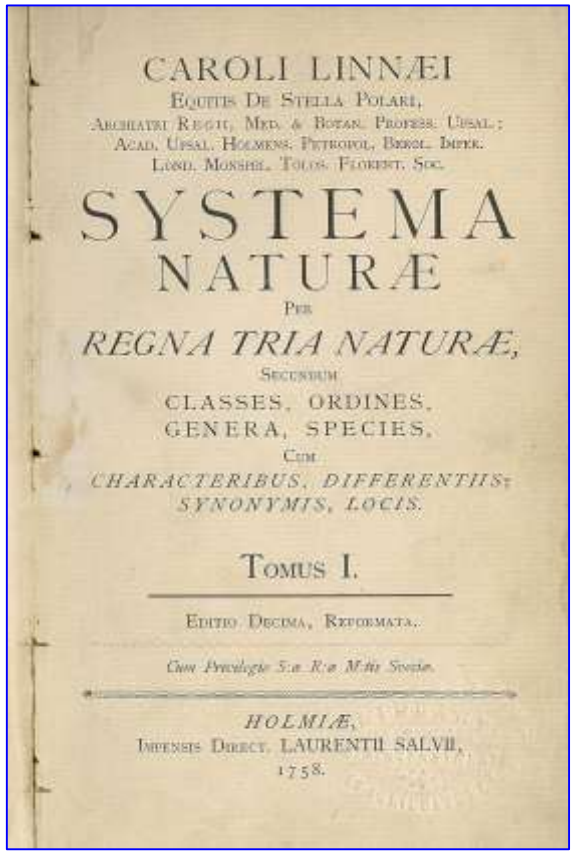
IN conducting the following Work, it is propofed to publifh the feven Orders, of which it conſiſts, ſeparately. The Orders, as ſtated Page 16, are characterized by the different Appearances







With the definition of histopathologic patterns, Ackerman unwittingly followed the examples of Carl Linnæus in botany and Robert Willan in clinical dermatology. The common goal was to facilitate recognition of biologic entities by creating a simple method of categorization. In that endeavor, all three authors focused on findings considered to be essential and distinguished them, in the Aristotelian tradition, from findings considered to be irrelevant or accidental. Linnæus focused on stamens and pistils, Willan on elementary skin lesions, and Ackerman on histopathologic patterns,



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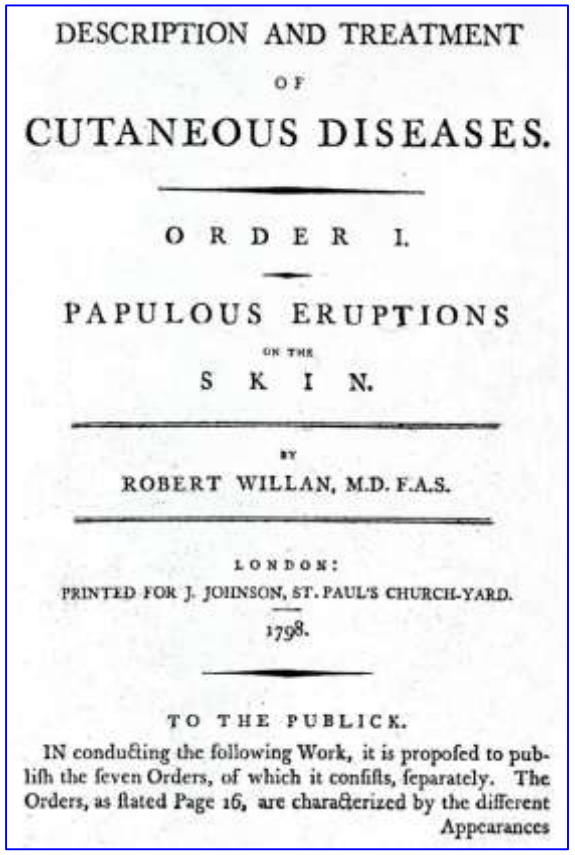

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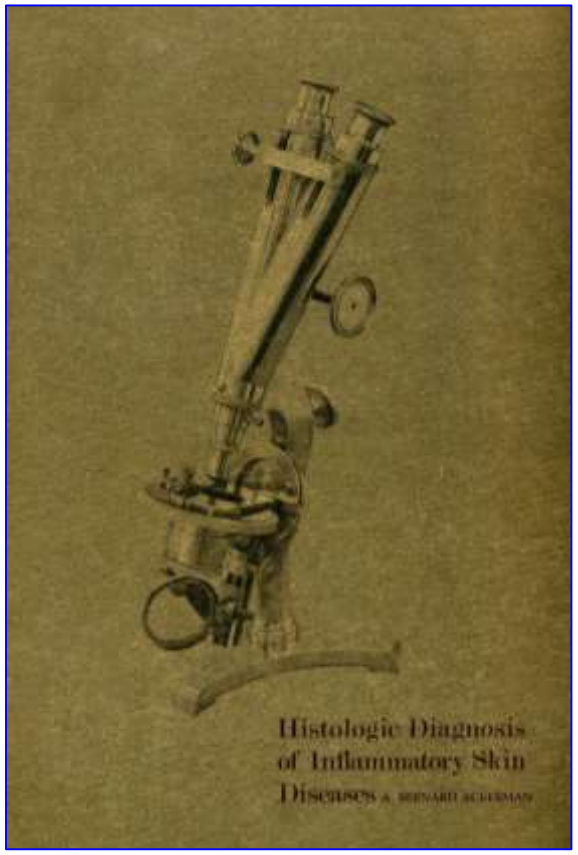
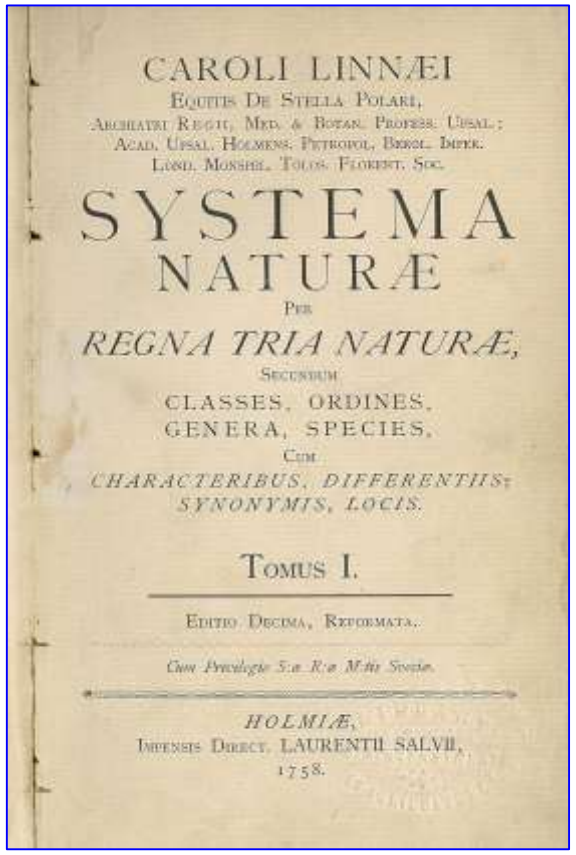


emphasizing that *"effective criteria for specific diagnosis of a disease capture the fewest denominators of it."* Reduction of a complex issue to a few easily identifiable criteria was common aspect of those identification schemes. Another was the importance attached to precise definition of those criteria.

Effective criteria for specific diagnosis of a disease capture the fewest denominators of it.

A. Bernard Ackerman, 1999



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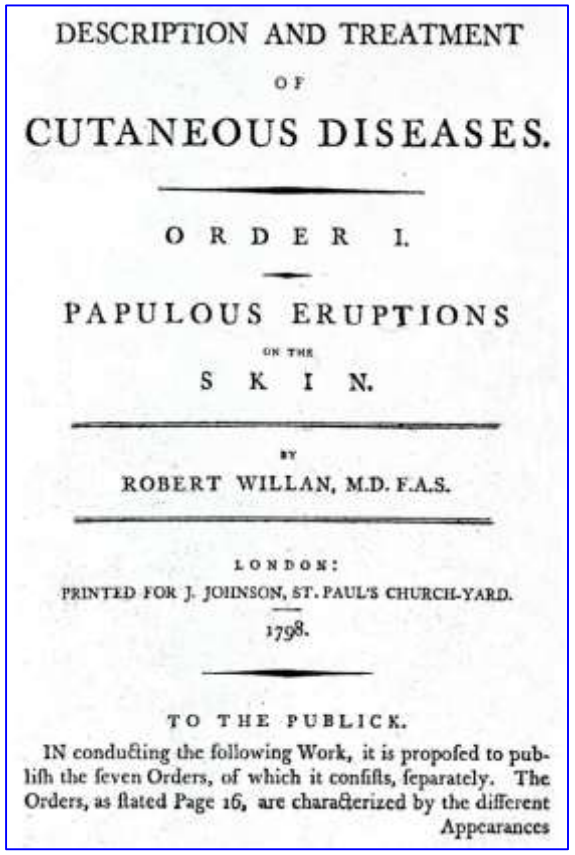

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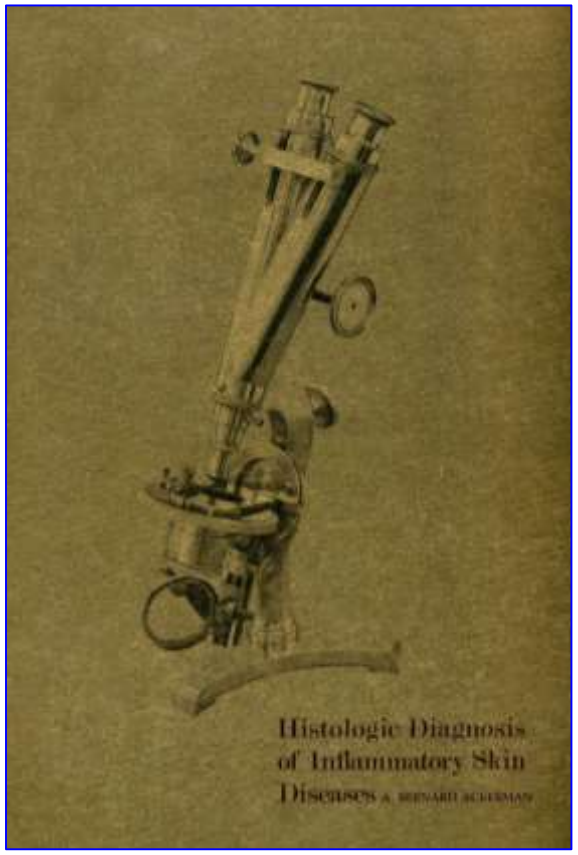
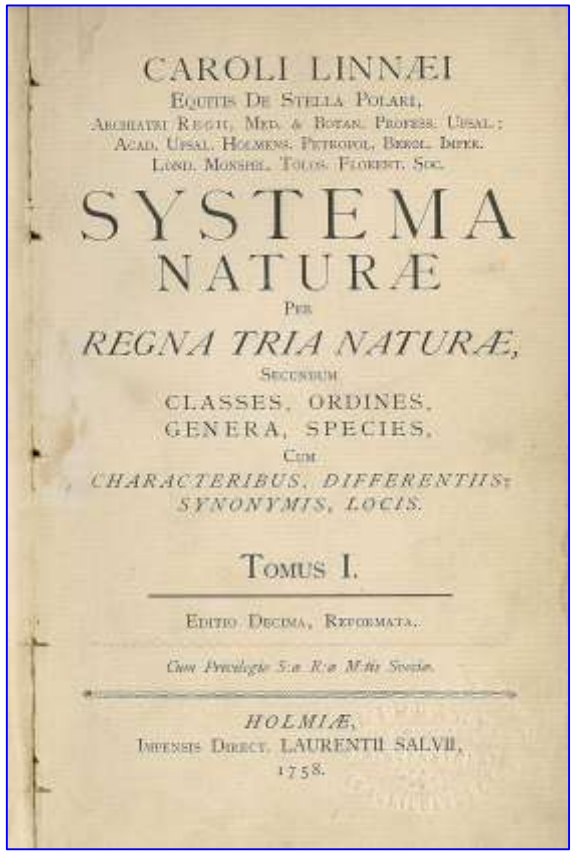


Already Willan noted, as his first and foremost desideratum, *"to fix the sense of the terms employed, by proper definitions,"* a stance diametrically opposed

… the desiderata …; 1. To fix the sense of the terms employed, by proper definitions.

Robert Willan, 1798



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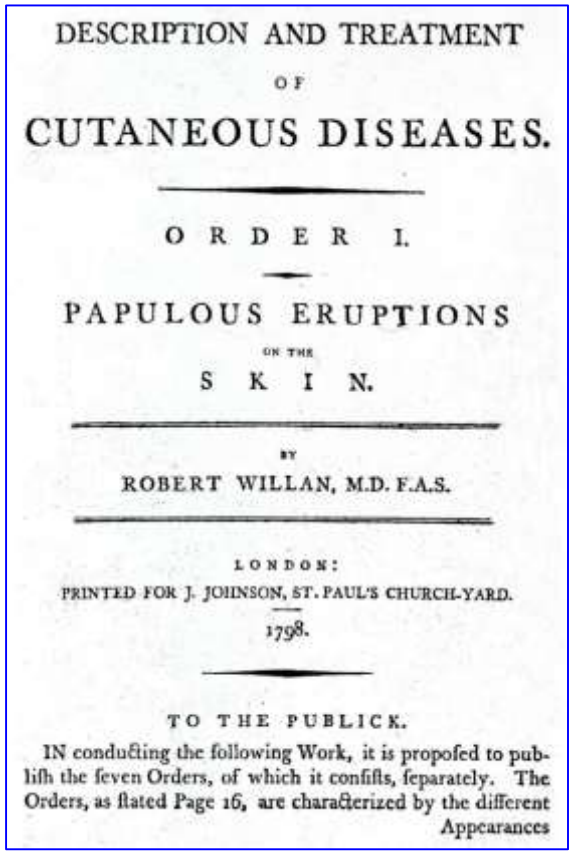

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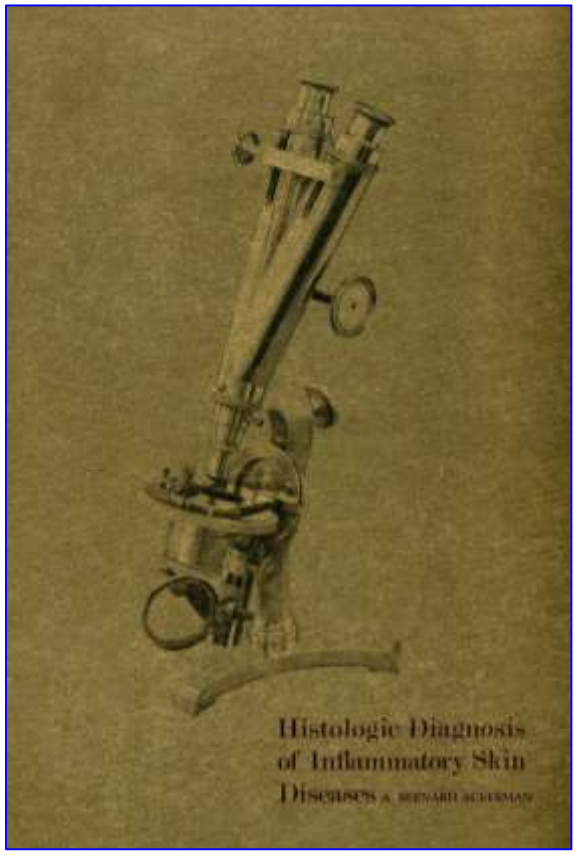
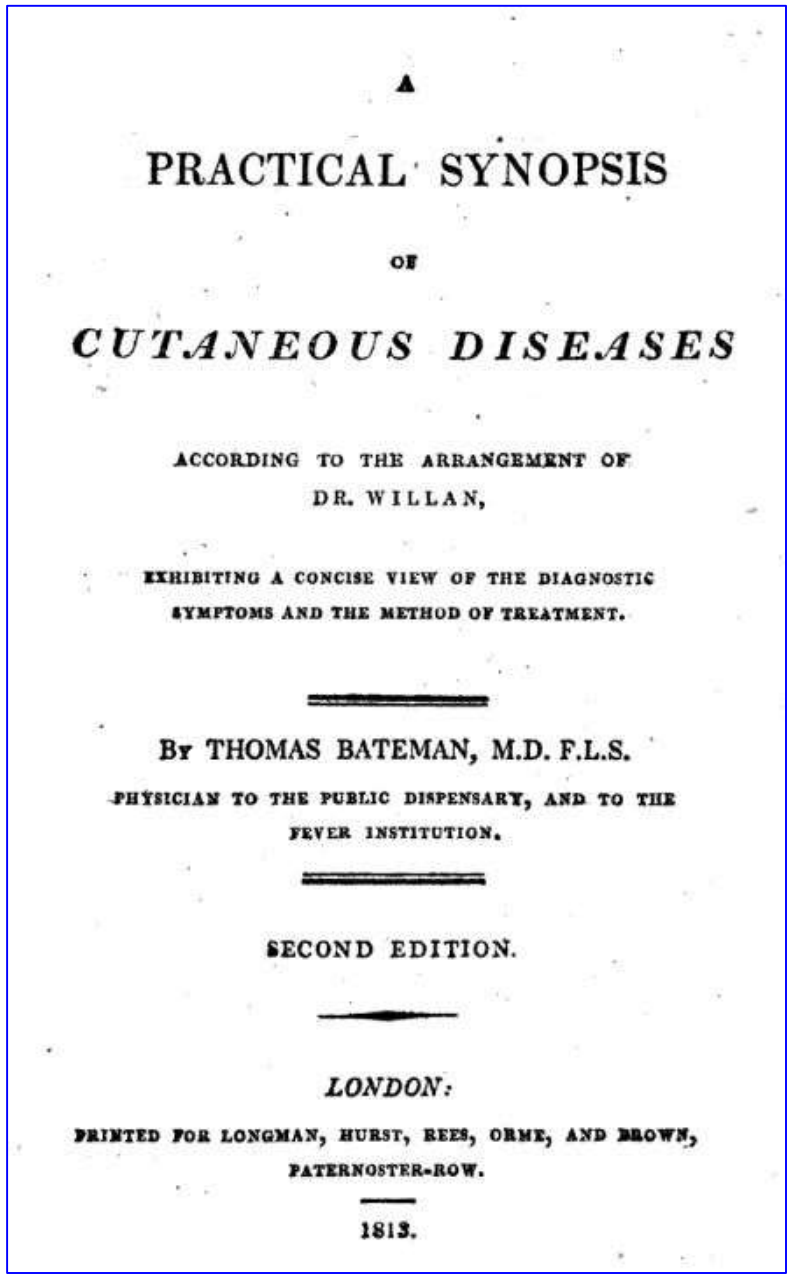


to the nominalistic attitude of Hutchinson according to whom *“names are good servants but poor masters.”*

Names are good servants
but poor masters.

Jonathan Hutchinson, 1896



A

PRACTICAL SYNOPSIS

OF

CUTANEOUS DISEASES

ACCORDING TO THE ARRANGEMENT OF
DR. WILLAN,

EXHIBITING A CONCISE VIEW OF THE DIAGNOSTIC
SYMPTOMS AND THE METHOD OF TREATMENT.

By THOMAS BATEMAN, M.D. F.L.S.

PHYSICIAN TO THE PUBLIC DISPENSARY, AND TO THE
FEVER INSTITUTION.

SECOND EDITION.

LONDON:

PRINTED FOR LONGMAN, HURST, REES, ORME, AND BROWN,
PATERNOSTER-ROW.

1813.

I am aware, indeed, that there are many individuals, professing themselves to be practical men, who affect a contempt for all nosological disquisitions, and deem the discussions relating to nomenclature, in particular, very idle and frivolous … But this I conceive to be a mistaken view of the subject … The inferences of slight and superficial observation may, indeed, be detailed without recourse to a very definite vocabulary; for where little discrimination is exercised, very little nicety can be requisite in regard to the import of the language employed. But it is not by such means that the boundaries of science are extended.

Thomas Bateman, 1813

In 1813, Willan's pupil Robert Bateman criticized the widespread disregard for a precise use of language in these words: *"I am aware, indeed, that there are many individuals, professing themselves to be practical men, who affect a contempt for all nosological disquisitions, and deem the discussions relating to nomenclature, in particular, very idle and frivolous … But this I conceive to be a mistaken view of the subject … The inferences of slight and superficial observation may, indeed, be detailed without recourse to a very definite vocabulary; for where little discrimination is exercised, very little nicety can be requisite in regard to the import of the language employed. But it is not by such means that the boundaries of science are extended."*

HISTOLOGIC CRITERIA FOR THE DIAGNOSIS OF SUPERFICIAL SPREADING MALIGNANT MELANOMA: FORMULATED ON THE BASIS OF PROVEN METASTATIC LESIONS

NORMAN M. PRICE, MB, ChB,* ARKADI M. RYWLIN, MD,† AND A. BERNARD ACKERMAN, MD‡

Histologic material was studied from 30 patients with metastasizing cutaneous superficial spreading malignant melanoma in an attempt to establish reproducible criteria for the accurate diagnosis of the disease. This paper details the criteria for the histologic diagnosis of primary superficial spreading malignant melanoma of the skin.

Cancer 38:2434–2441, 1976.

DURING THE PAST DECADE NEW AND IMPORTANT information has been gleaned by careful gross and histologic study of primary malignant melanoma in skin. Clark, et al.[5] and McGovern[19] have identified three morphologic types of malignant melanoma; superficial spreading melanoma, lentigo maligna melanoma, and nodular melanoma. They have also suggested prognostic criteria based, not only upon the type of melanoma, but also upon the depth of extension of malignant melanocytes into the dermis. These authors did not deal with the problem of distinguishing malignant melanomas from benign melanocytic lesions.

The histologic diagnosis of malignant melanoma is still fraught with difficulty in some cases. Despite the new classification of Clark and McGovern, malignant melanoma is occasionally misdiagnosed histologically as a benign melanocytic nevus, and some cases of nevi are incorrectly interpreted as malignant melanomas.[11] Helwig[9] wrote that 38% of a group of pathologists misdiagnosed a spindle and epithelioid cell nevus (juvenile melanoma) as a malignant melanoma, and Traux[26] stated that 25% of 247 cases of malignant melanoma in the Connecticut Tumor Registry had been misdiagnosed.

Our study was designed to establish criteria for the histologic differentiation of superficial spreading malignant melanoma from other melanocytic lesions. In order to be certain that we had excluded lesions which were not indubitable malignant melanomas, we studied only those cases in which there were adequate specimens of tissue from primary lesions and metastases therefrom. Few previous attempts to establish such histologic criteria[1,3,5,7,8,20] have dealt with primary cutaneous melanomas whose biologic malignancy was established by the presence of metastases.

MATERIALS AND METHODS

Cancer Registry listings from 1960–1972 of patients with malignant melanoma from the University of Miami Hospitals (Jackson Memorial, Veterans Administration, and Mount Sinai) were investigated. A similar group of patients was gathered from the files of the Malignant Melanoma Clinical Cooperative Group Study at the New York University Medical Center for the time period 1972–1974. The Miami area group numbered 150 patients, and the New York area group 140 patients. Because only those patients were incorporated into the study from whom there was adequate histologic material of both a primary cutaneous and a metastatic lesion of malignant melanoma, our eventual total was 31 patients from the Miami group and 19 patients from the New York group. From this combined total of 50 patients, four were excluded because they were lentigo maligna melanomas, and 13 were excluded because they were nodular melanomas. Of the remaining 33, all of which were superficial spreading melanomas, three could not be utilized in the study because adequate histological sections from the primary tumors were not available.

From the * Department of Dermatology, † The Departments of Dermatology and Pathology, New York University Medical Center, New York City, New York; and the ‡ Department of Pathology, Mount Sinai Medical Center, and the University of Miami School of Medicine, Miami, Florida.

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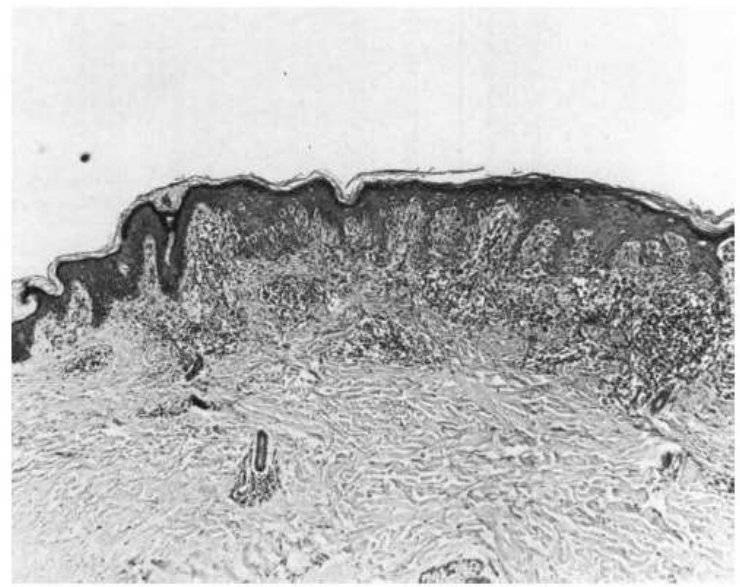

FIG. 1. Lateral extension of atypical melanocytes at the periphery of a lesion of superficial spreading malignant melanoma (H & E, ×10).

By focusing on findings germane to a specific diagnosis and by translating them into a set of clearly defined criteria, boundaries of science were extended. One example is the first study concerning histopathologic criteria for diagnosis of melanoma *"formulated on the basis of proven metastastic lesions."*

HISTOLOGIC CRITERIA FOR THE DIAGNOSIS OF SUPERFICIAL SPREADING MALIGNANT MELANOMA: FORMULATED ON THE BASIS OF PROVEN METASTATIC LESIONS

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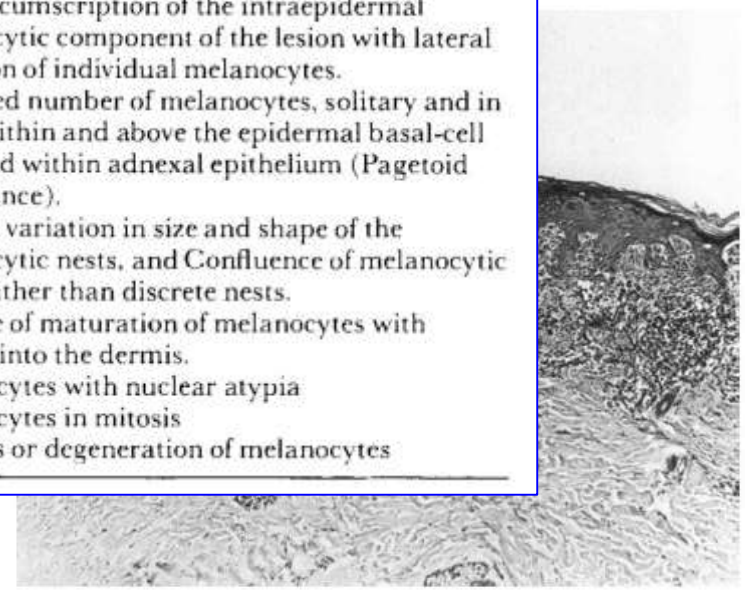

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All observations were condensed to seven criteria that allowed melanomas to be distinguished from nevi. Once recognition had been improved, those findings helped to define the disease better, a phenomenon

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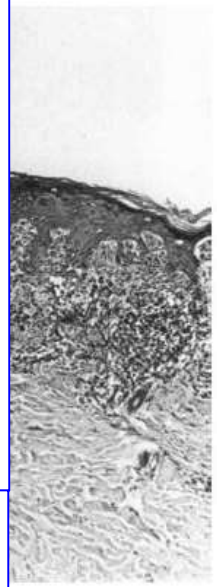

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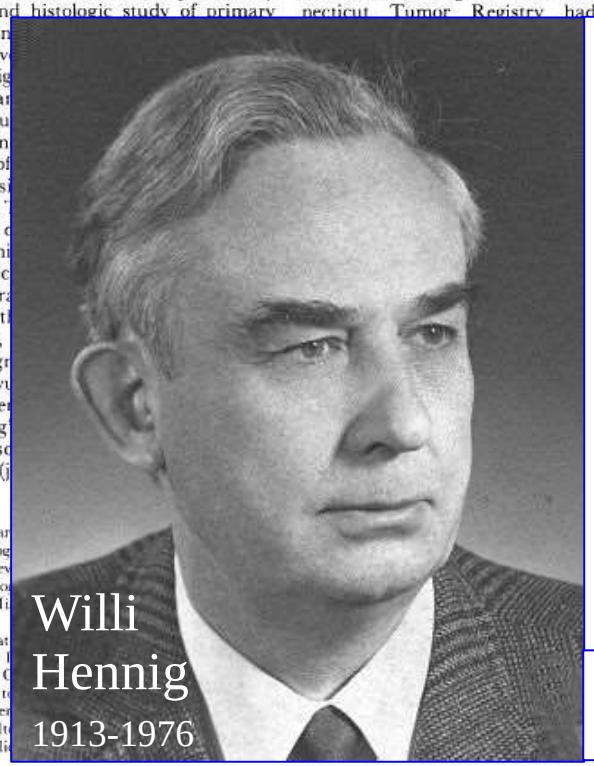

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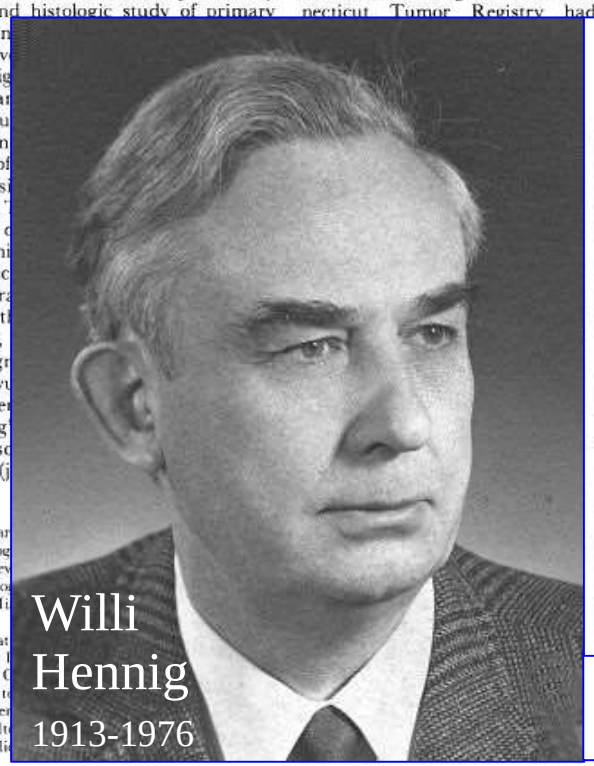

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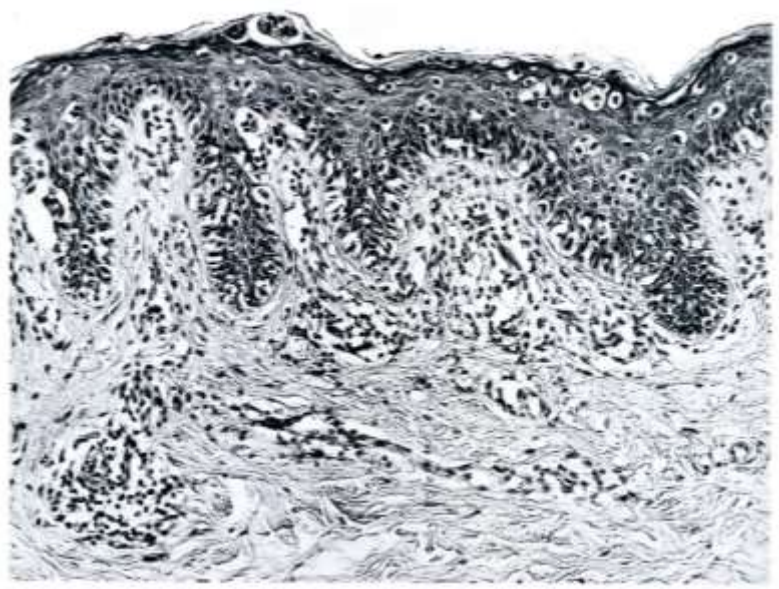

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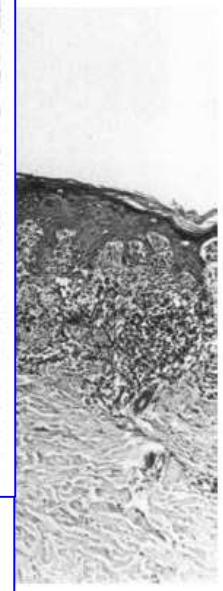

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The American Journal of Dermatopathology
Volume 1, Number 1
Spring 1979

Jorge L. Sanchez, M.D.

A. Bernard Ackerman, M.D.

The patch stage of mycosis fungoides

Criteria for histologic diagnosis

ABSTRACT It has long been claimed that a specific histologic diagnosis of mycosis fungoides cannot be made in the "premycotic" or "eczematous" (patch) stage of the disease. Indeed, the histologic features of the premycotic lesions were constantly said to be those of "chronic non-specific dermatitis."

We studied 46 biopsy specimens of patch lesions from patients in whom mycosis fungoides was unequivocally established by clinical events (i.e., concurrence or later development of typical plaque and/or nodular lesions) and indubitable histologic findings. We divided patch lesions into early nonatrophic patches and late atrophic ones. The early patches are considered to be evolving lesions of mycosis fungoides, whereas late patches represent resolving plaques of the disease. On the basis of this study, we concluded that histologic diagnosis can be made with near certainty in patch lesions of the disease. We found that the critical feature for histologic diagnosis of early and late patch lesions of mycosis fungoides is the presence of an increased number of mononuclear cells distributed singly or in small collections within an epidermis devoid of spongiotic microvesiculation. Other important features are lacunae surrounding intraepidermal mononuclear cells which gives them the appearance of "haloed cells." A sparse infiltrate of mononuclear cells is present around the blood vessels of the superficial, and sometimes the deep, vascular plexus. Atypical mononuclear cells are not necessary for the diagnosis of early patch lesions of mycosis fungoides, but they are found commonly in late patch lesions. Late atrophic patches show a thinned epidermis, loss of the usual configuration between rete ridges and dermal papillae, and coarse collagen throughout a thickened papillary dermis.

From the Department of Dermatology of the University of Puerto Rico School of Medicine, San Juan, Puerto Rico (JLS), and the Departments of Dermatology and Pathology, New York University School of Medicine (ABA).

"In the premycotic stage of mycosis fungoides, the clinical picture may be more suggestive than the histopathologic picture, which usually shows chronic dermatitis."[1]
W. Caro, 1978

"The earliest histologic changes in mycosis fungoides are usually those of a mild, chronic, non-specific dermatitis."[2]
H. S. Zackheim and E. Epstein, Jr., 1978

"In the premycotic stage [of mycosis fungoides] the lesions are most often non-specific."[3]
E. Brehmer-Anderson, 1976

"Sometimes in the early stages of the classical form of mycosis fungoides and occasionally for many years, the changes are entirely non-specific."[4]
P. D. Samman, 1976

"Must I diagnose mycosis fungoides? If the diagnosis of mycosis fungoides is delayed several months or even a few years in a questionable class, little is lost, and much may be gained by avoiding diagnostic error."[5]
H. Pinkus, 1976

"In the erythematous stage of mycosis fungoides, a specific diagnosis of the disease cannot be made."[6]
W. F. Lever, 1975

"In the earliest stages [of mycosis fungoides] all the changes may not be evident. The microscopic diagnosis in the first or eczematoid stage is difficult or sometimes impossible since the changes are in many ways similar to those observed in eczematoid dermatitis and neurodermatitis."[7]
E. B. Helwig, 1972

"A sine qua non of this [early] phase [of mycosis fungoides] is that a diagnosis of malignant reticulosis cannot be established by histopathologic examination."[8]
Clendening, 1971

"Early lesions of mycosis fungoides show a non-specific dermatitis."[9]
H. Montgomery, 1966

For decades past, most pathologists have averred that the histologic changes in early lesions of mycosis fungoides are nonspecific and nondiagnostic. Dermatologists, too, have found it difficult to make sure clinical diagnoses of mycosis fungoides from early lesions and instead speak with uncertainty of a "premycotic" or "eczematous" stage of this disease.

We undertook a study as a test of the consensus that early lesions of mycosis fungoides cannot be recognized clinically and histologically with surety. We concluded, and hope to convince readers, that the gross and microscopic pathology of mycosis fungoides can be identified from the earliest patch lesions of the disease. What follows is the evidence we have for this conclusion and conviction.

MATERIALS AND METHODS

Seventy patients with mycosis fungoides proved by typical clinical pictures, i.e., plaques and nodules, and by characteristic histologic features constitute this series. Eighteen of these patients were followed in the Section of Dermatology of the University of Puerto Rico; 23 of them were seen at the Department of Dermatology of the New York University School of Medicine; and 29 were patients from private physicians whose biopsies were read in the Dermatopathology Section of the New York University School of Medicine between 1975 and 1978. A total of 106 biopsy specimens were obtained from these 70 patients. Of these, 46 came from patches, 45 from plaques, and 15 from nodules.

All specimens were processed in the routine manner and stained by hematoxylin and eosin. Perl's stain was done for hemosiderin and Verhoeff's Van Gieson stain for elastic tissue.

Clinical photographs were taken of many of these patients in order to better correlate the histologic and gross pathological features.

Clinical information such as duration of the disease, age of lesions, staging, and management were obtained on every patient and are presented in Tables 1 and 2.

TABLE 1.
Duration of the Disease

Age	Number of Patients
0–1 year	6
1–5 years	25
6–10 years	10
11–20 years	12
>20 years	3
Unknown	6

FIGURE 1
Early patch of mycosis fungoides. This broad, irregularly-shaped, reddish, flat lesion shows no evidence of atrophy clinically and is therefore an evolving lesion of mycosis fungoides.

TABLE 2.
Stages of the Disease

	Number of Patients
Stage I	10
Stage II	34
Stage III	10
Stage IV	0
Stage VA	3
Stage VB	1
Undetermined	6

Likewise, Sánchez and Ackerman in 1979 set forth criteria for histologic diagnosis of the patch stage of mycosis fungoides, studying *"patch lesions from patients in whom mycosis fungoides was unequivocally established by clinical events."* The results of this study changed the perception of the disease

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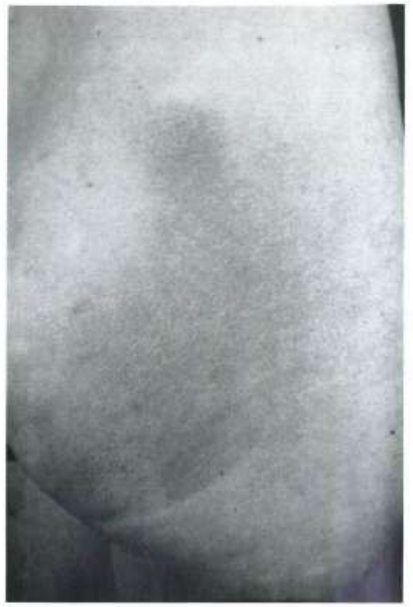

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Stage I	10
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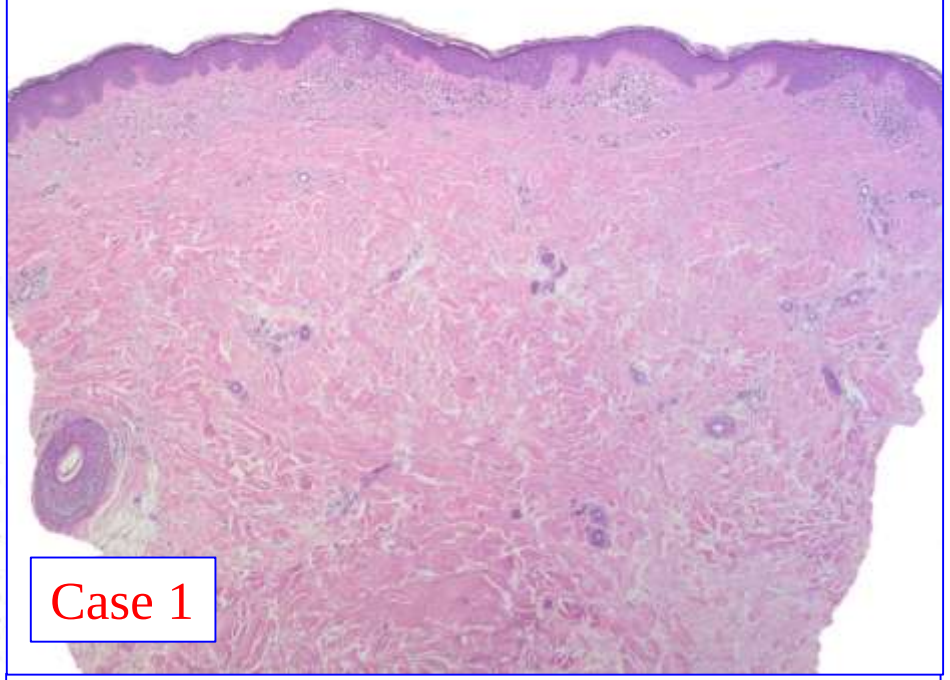


Case 1

"reciprocal illumination"

through *"reciprocal illumination."* Because mycosis fungoides could be diagnosed reliably in the early patch stage, as in our case 1, it became evident that it usually takes an uneventful course over many years.

The American Journal of Dermatopathology
Volume 1 · Number 1
Spring · 1979

Jorge L. Sanchez, M.D.

A. Bernard Ackerman, M.D.

The patch stage of mycosis fungoides

Criteria for histologic diagnosis

ABSTRACT It has long been claimed that a specific histologic diagnosis of mycosis fungoides cannot be made in the "premycotic" or "eczematous" (patch) stage of the disease. Indeed, the histologic features of the premycotic lesions were constantly said to be those of "chronic nonspecific dermatitis."

We studied 46 biopsy specimens of patch lesions from patients in whom mycosis fungoides was unequivocally established by clinical events (i.e., concurrence or later development of typical plaque and/or nodular lesions) and indubitable histologic findings. We divided patch lesions into early nonatrophic patches and late atrophic ones. The early patches are considered to be evolving lesions of mycosis fungoides, whereas late patches represent resolving plaques of the disease. On the basis of this study, we concluded that histologic diagnosis can be made with near certainty in patch lesions of the disease. We found that the critical feature for histologic diagnosis of early and late patch lesions of mycosis fungoides is the presence of an increased number of mononuclear cells distributed singly or in small collections within an epidermis devoid of spongiotic microvesiculation. Other important features are lacunae surrounding intraepidermal mononuclear cells which gives them the appearance of "haloed cells." A sparse infiltrate of mononuclear cells is present around the blood vessels of the superficial, and sometimes the deep, vascular plexus. Atypical mononuclear cells are not necessary for the diagnosis of early patch lesions of mycosis fungoides, but they are found commonly in late patch lesions. Late atrophic patches show a thinned epidermis, loss of the usual configuration between rete ridges and dermal papillae, and coarse collagen throughout a thickened papillary dermis.

From the Department of Dermatology of the University of Puerto Rico School of Medicine, San Juan, Puerto Rico (JLS), and the Departments of Dermatology and Pathology, New York University School of Medicine (ABA).

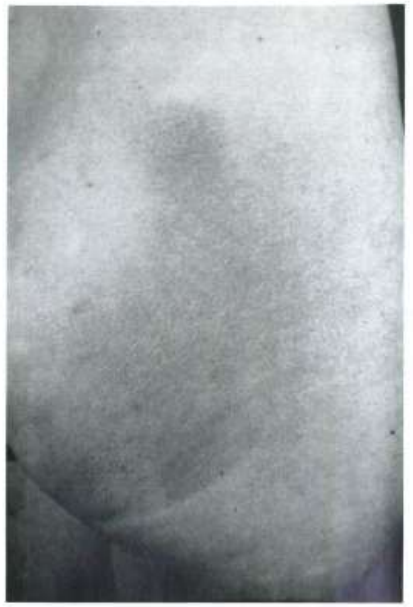
"A sine qua non of this [early] phase [of mycosis fungoides] is that a diagnosis of malignant reticulosis cannot be established by histopathologic examination."[8]

Clendening, 1971

"Early lesions of mycosis fungoides show a non-specific dermatitis."[9]

H. Montgomery, 1966

For decades past, most pathologists have averred that the histologic changes in early lesions of mycosis fungoides are nonspecific and nondiagnostic. Dermatologists, too, have found it difficult to make sure clinical diagnoses of mycosis fungoides from early lesions and instead speak with uncertainty of a "premycotic" or "eczematous" stage of this disease.



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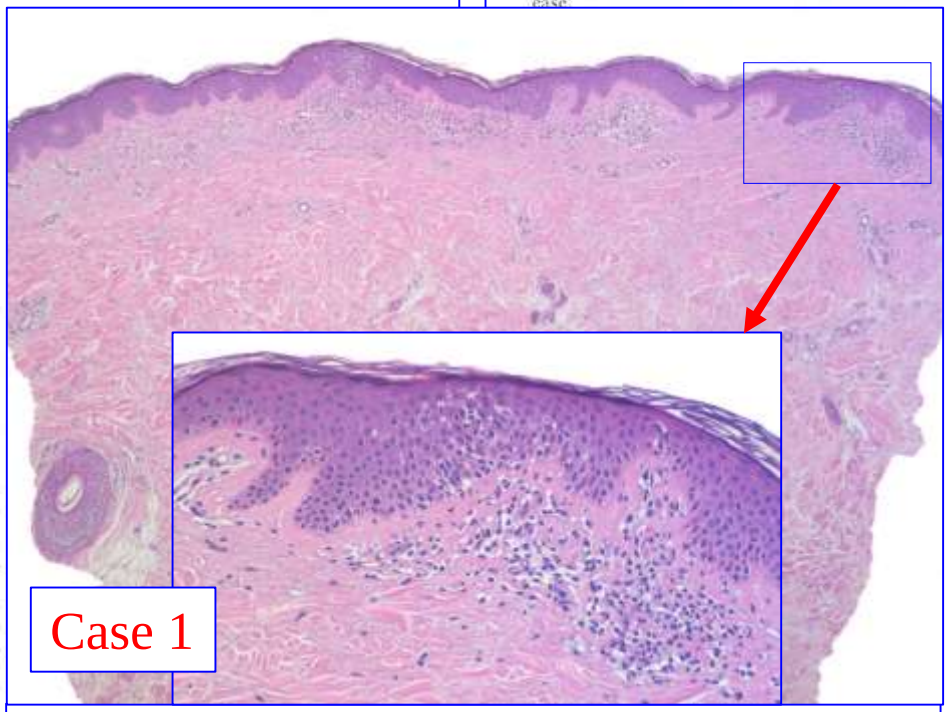

Case 1

"reciprocal illumination"

Moreover, because of the same characteristic findings, such as lymphocytes peppering the epidermis in concert with scant spongiosis, lymphocytes aligned in the basal layer, and coarse collagen in the papillary dermis, parapsoriasis en plaques has become accepted as a manifestation of mycosis fungoides, rather than a differential diagnosis of it. Case 1 is a classical example.

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Diagnosis by Histopathologic Patterns

Recognition of Major Patterns

- Superficial perivascular dermatitis
- Superficial and deep perivascular dermatitis
- Vasculitis
- Nodular and diffuse dermatitis
- Intraepidermal vesicular and pustular dermatitis
- Subepidermal vesicular dermatitis
- Folliculitis and perifolliculitis
- Fibrosing dermatitis
- Panniculitis

Advantages of Pattern Method

Application of Pattern Method

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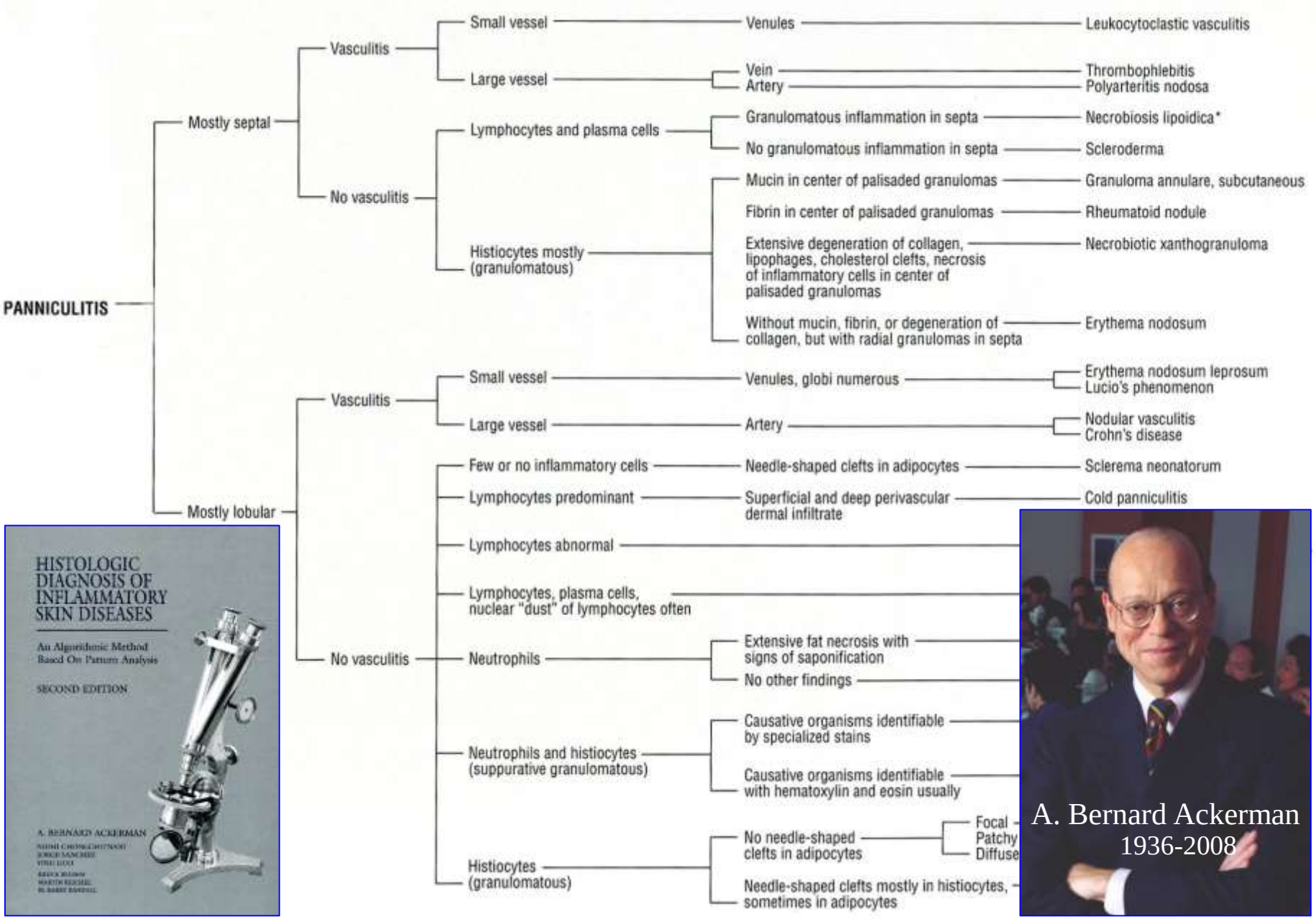
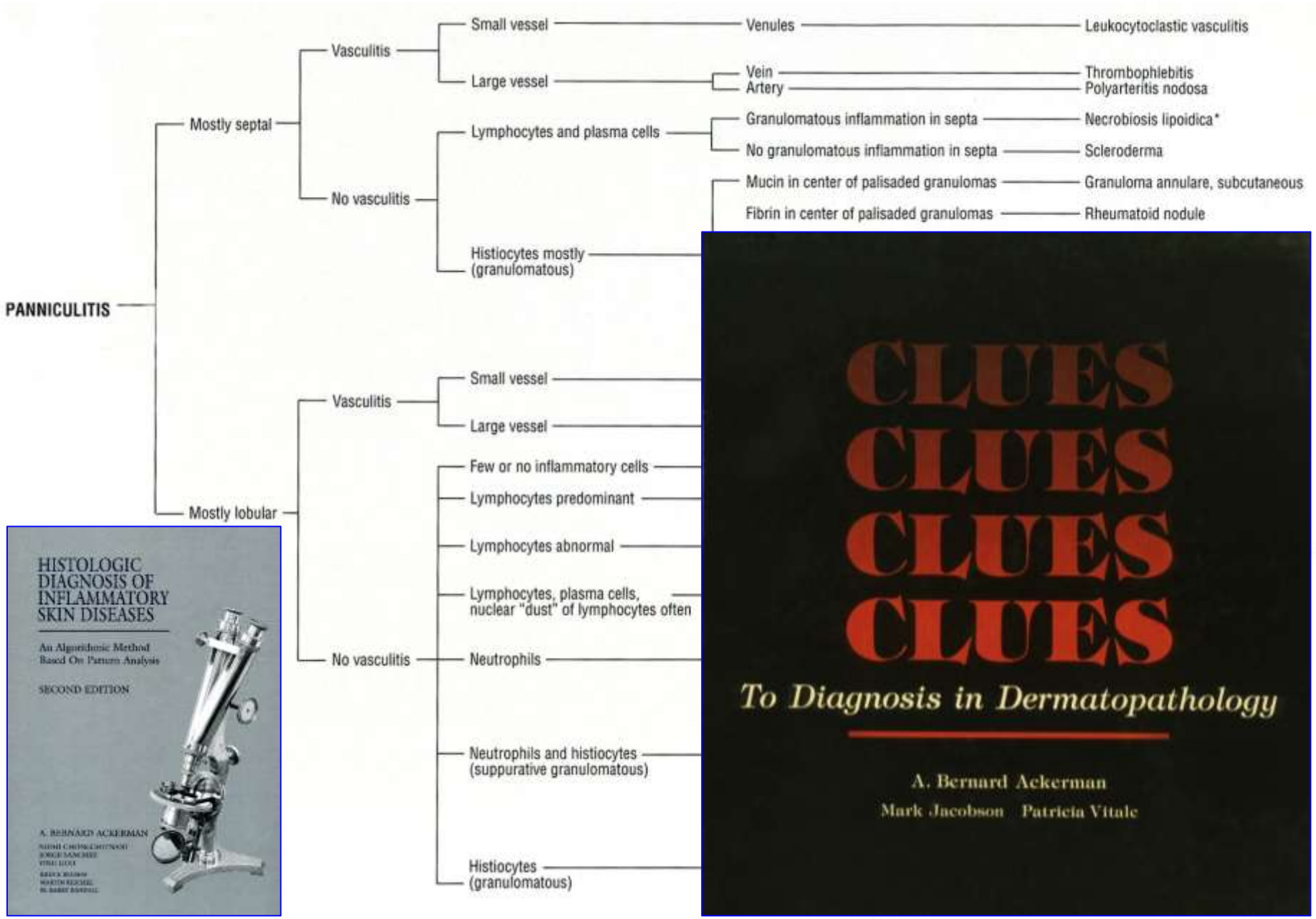
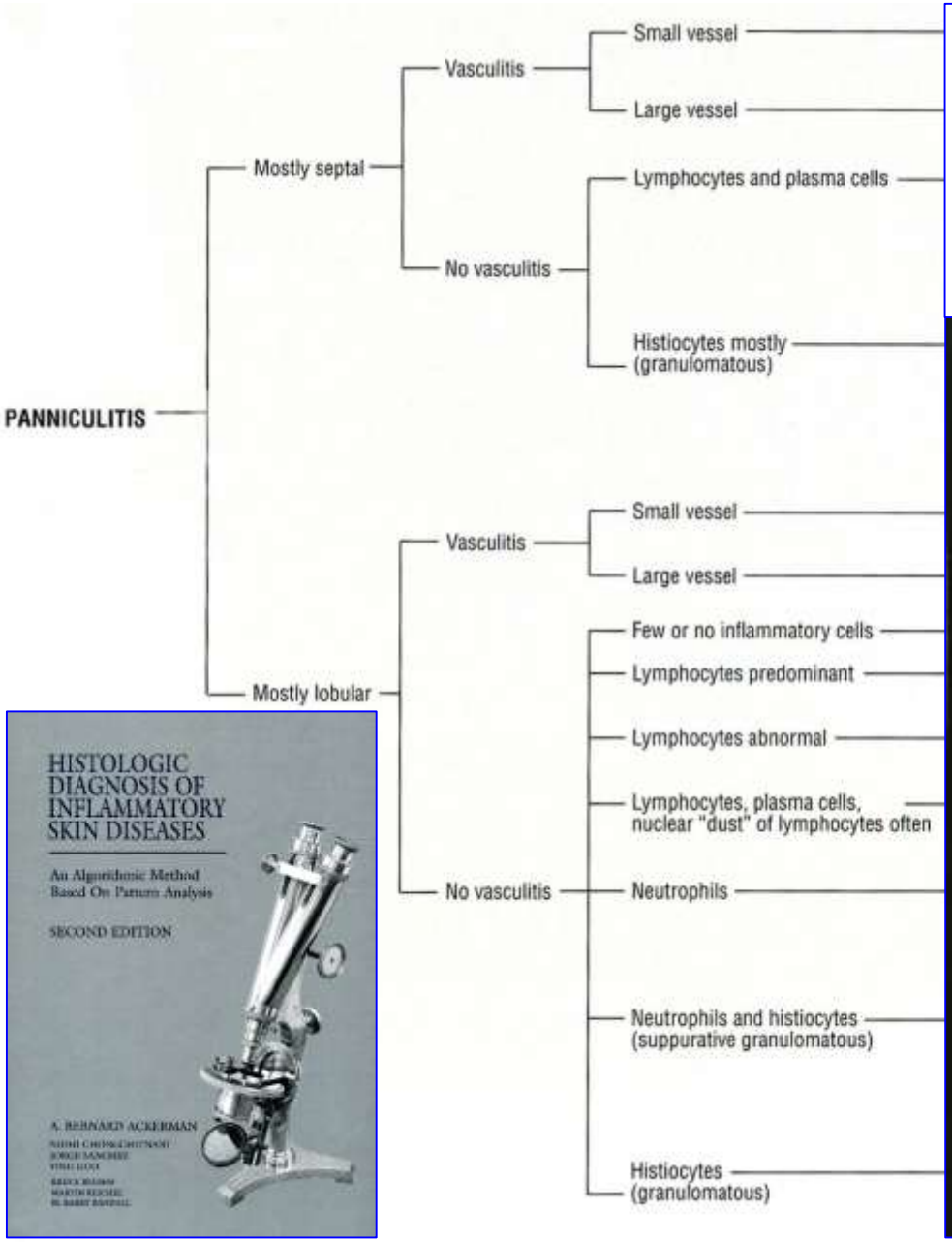
Through pattern analysis and the establishment of reproducible criteria for diagnosis, dermatopathology was transformed from a descriptive into an analytic science.



Eventually, pattern analysis was supplemented by algorithms, that were based on the method of classification introduced by Plato, namely, binary division of contraries,

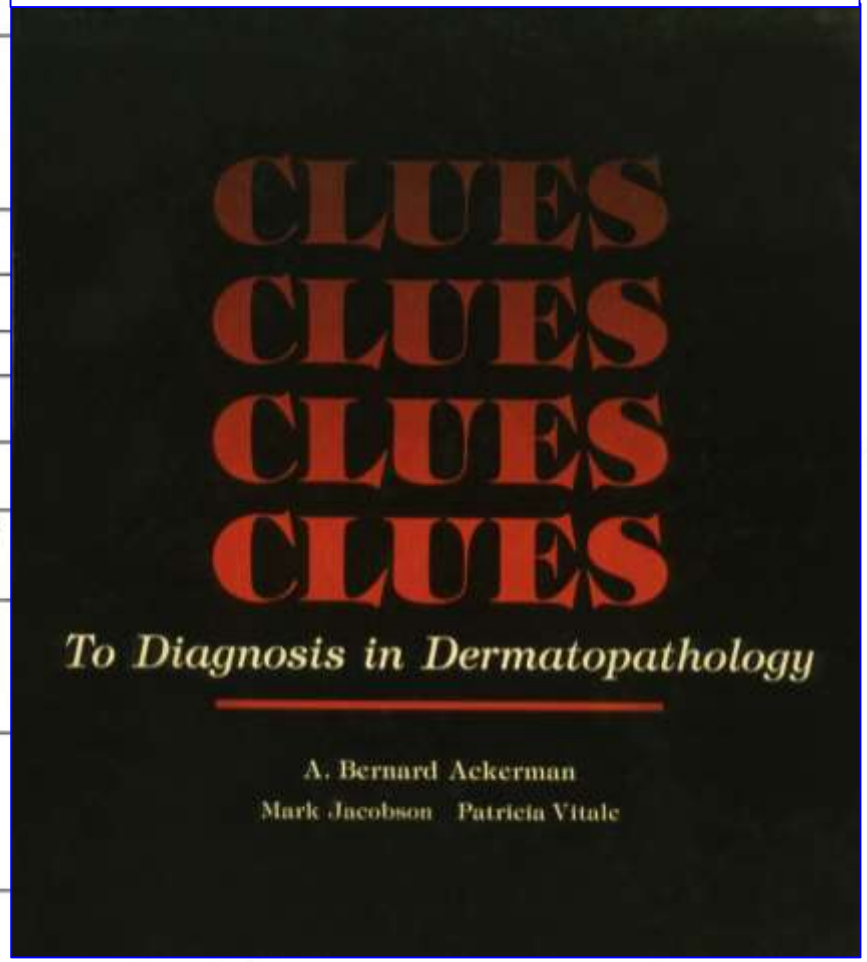


and by a contrasting approach through clues, i.e., minute findings diagnostic of a specific entity. However, despite some progress through *"reciprocal illumination,"* the focus was on identification, rather than definiton, of entities.

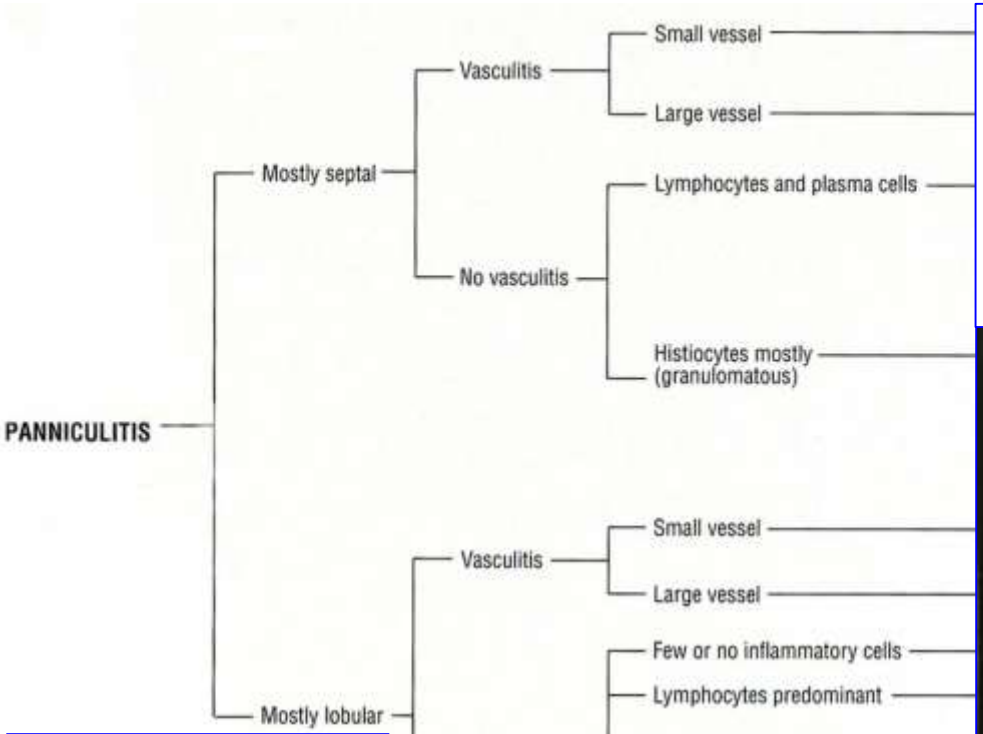


Effective criteria for specific diagnosis of a disease capture the fewest denominators of it.

A. Bernard Ackerman, 1999



For the latter purpose, the condensing approach of capturing *"the fewest denominators"* of a complex biologic process is unsuitable.



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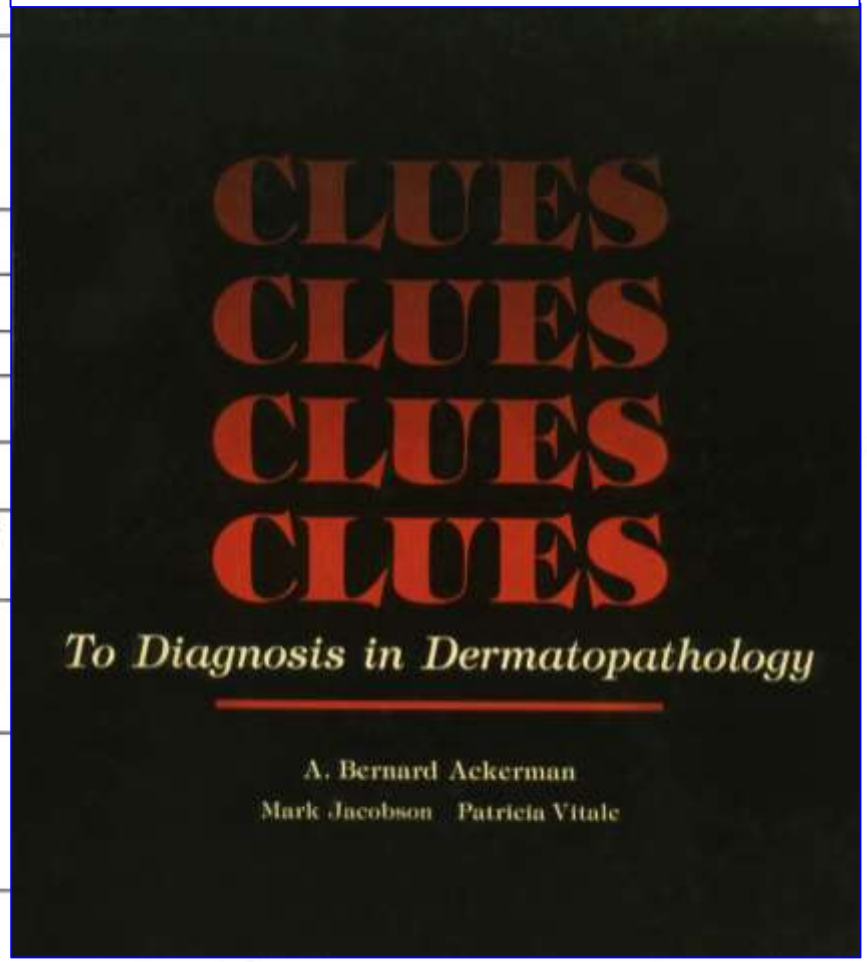
We must make use of all parts of the object which we have under consideration.

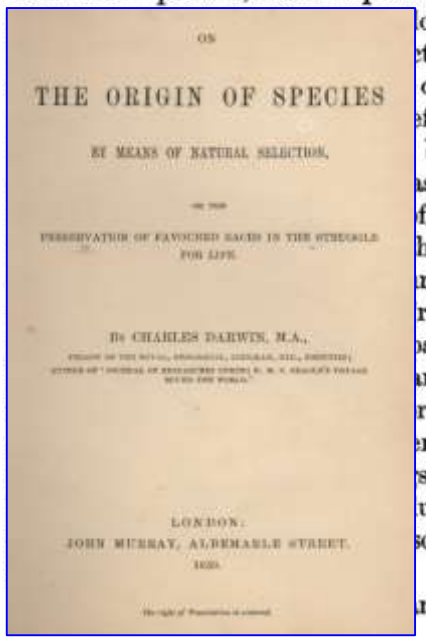
Georges-Louis Leclerc de Buffon, 1749



Already Buffon insisted that, for a biologic classification, we *"must make use of all parts of the object which we have under consideration,"*

birds and reptiles, as an approach in structure in any one internal and important organ.

The importance, for classification, of trifling characters, mainly depends on their being correlated with several other characters of more or less importance. The value indeed of an aggregate of characters is very evident in natural history. Hence, as has often been remarked, a species may depart from its allies in several characters, both of high physiological importance and of almost universal prevalence, and yet leave us in no doubt where it should be ranked. Hence, also, it has been found, that a classification founded on any single character, however important that may be, has always failed; for no part of the organisation is universally constant. The importance of an aggregate of characters, even when none are important, alone explains, I think, that saying


ON

THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

By CHARLES DARWIN, M.A.,

LONDON:
JOHN MURRAY, ALBEMARLE STREET.

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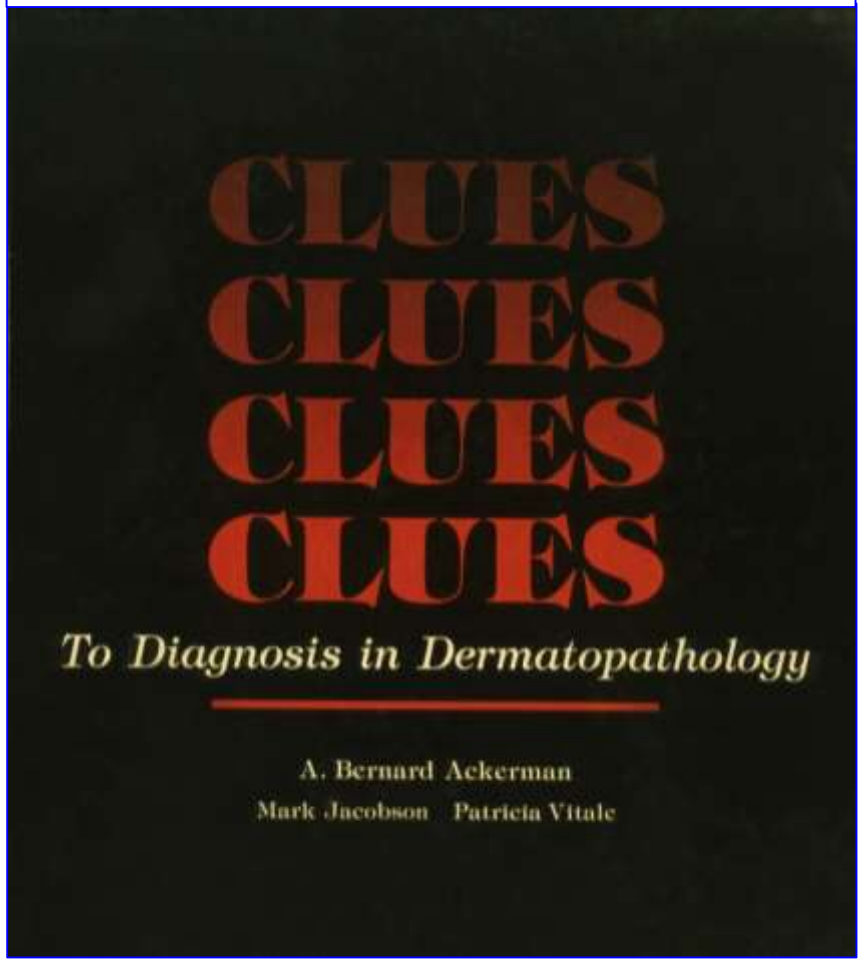

and Darwin emphasized the importance of *"an aggregate of characters"* for any biological classification.
This applies to medicine just as to zoology and botany, and it was ackowledged by Ackerman in regard to "clues":

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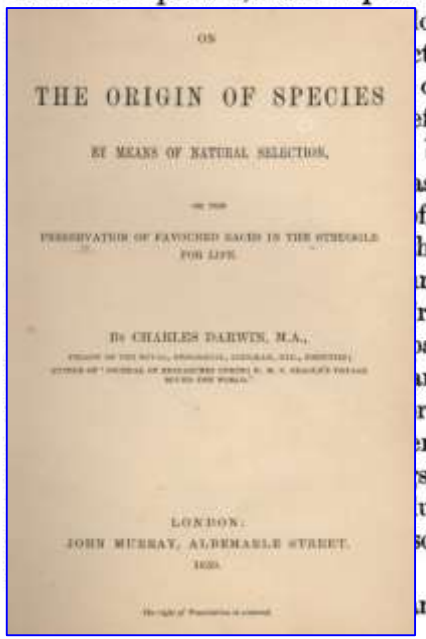
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THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

OR THE

PRESERVATION OF FAVOURED RACES IN THE STRUGGLE FOR LIFE.

By CHARLES DARWIN, M.A.,

LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1859.

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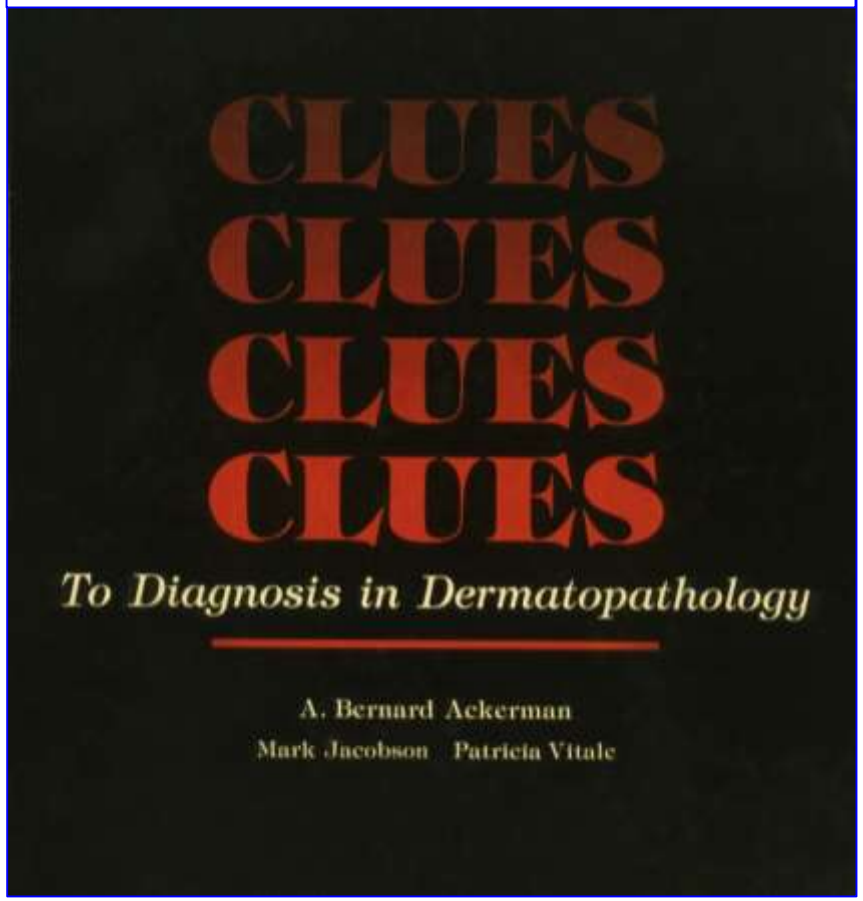

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The language of clinical dermatology is important because it is, or should be, the language of the disease as a whole, rather than merely aspects or patterns of it, and this requires the integration of all findings. The reason is that in biology, unlike physics, there are exceptions to almost every rule, and the more one relies on the rule, the more one may be fooled by exceptions. "

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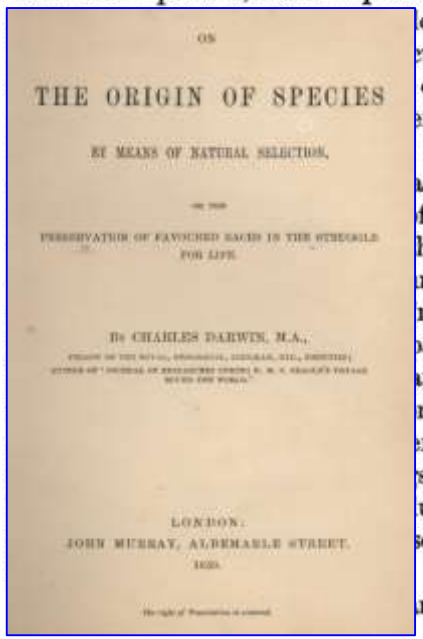
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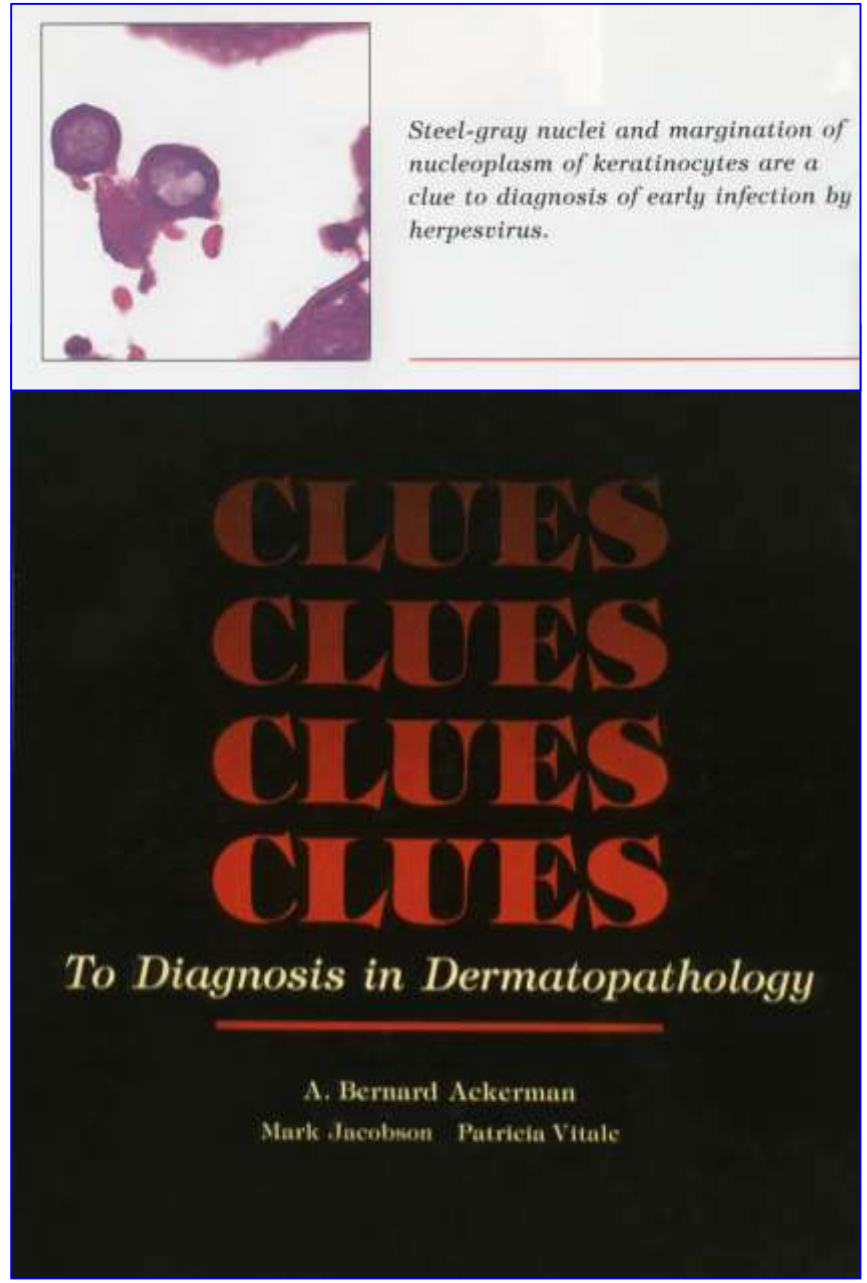

For example, *"steel-gray nuclei and margination of nucleoplasm of keratinocytes are a clue to diagnosis of early infection by herpesvirus."*

Pseudoherpetic Grover Disease: Report of 2 Cases and Review of the Literature

Ginger L. Wiersma, BS, Arturo P. Saavedra, MD, PhD, MBA,†‡§ F. Clarissa Yang, MD,‡ Tina R. Nandi, MD,‡ Danielle Levine, MD,¶ and George F. Murphy, MD†‖*

Abstract: Two cases of a pseudoherpetic variant of Grover disease are presented. The first patient was a 60-year-old woman who had high fevers in combination with right lower lobe pneumonia. She developed an itchy papulovesicular rash on her back and upper abdomen. The second patient was a 68-year-old woman who while bedridden developed an itchy papulovesicular rash
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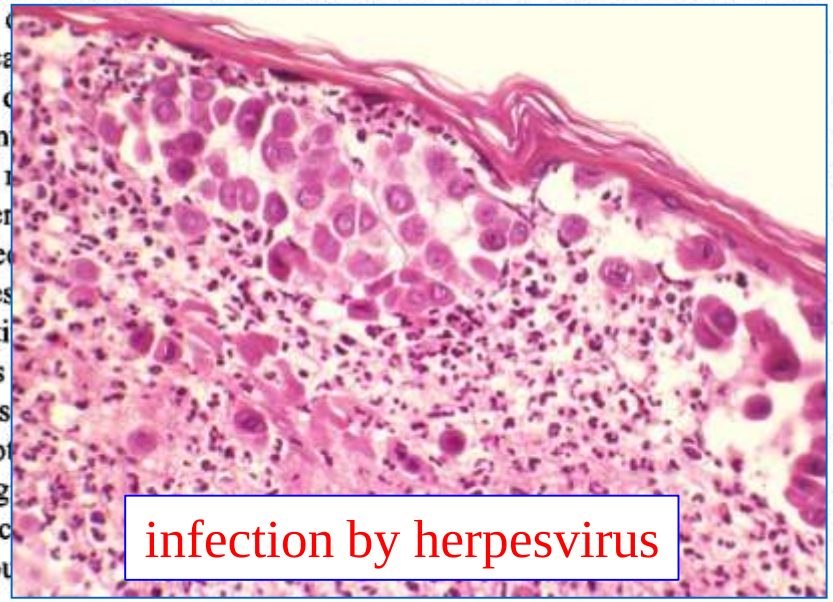
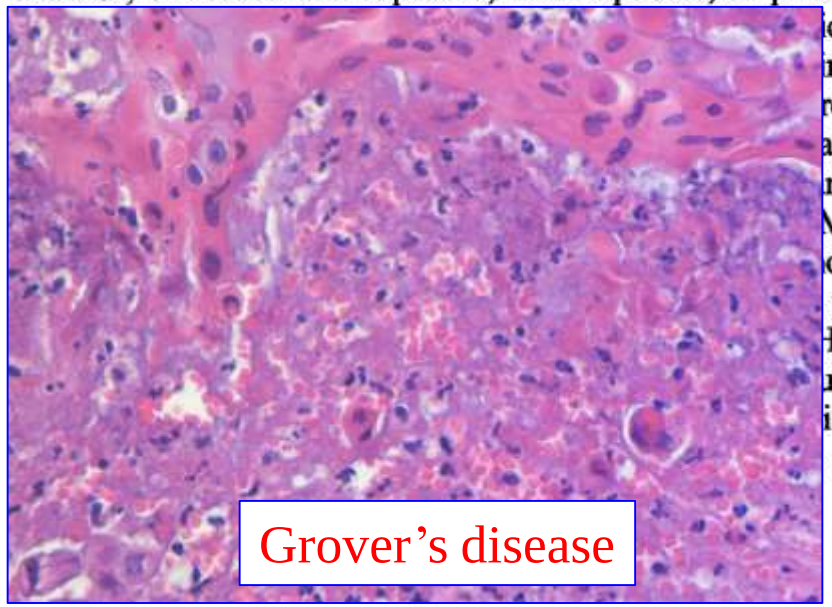


infection by herpesvirus

Key Words: Grover disease, acantholytic dermatosis, pseudoherpetic, vesicular variant, dyskeratosis

(*Am J Dermatopathol* 2014;36:746–750)

vesicles and even bullae are seen. The current diagnostic criteria for Grover disease involve both clinical and pathological features. Clinical lesions are pruritic, erythematous, nonfollicular crusted papules and papulovesicles located primarily on the trunk. Etiologic factors that have been hypothesized as either causal or precipitating include heavy sweat-inducing exercise, excessive sun exposure, heat exposure, or persistent



Grover's disease

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Patient 1

The first patient was a 60-year-old woman who developed a mildly pruritic rash on her back 2 days after initiation of treatment with azithromycin for right lower lobe

Very similar findings, however, are sometimes encountered in Grover's disease, an exceptional phenomenon that has been referred to as "pseudo-herpetic Grover's disease,"

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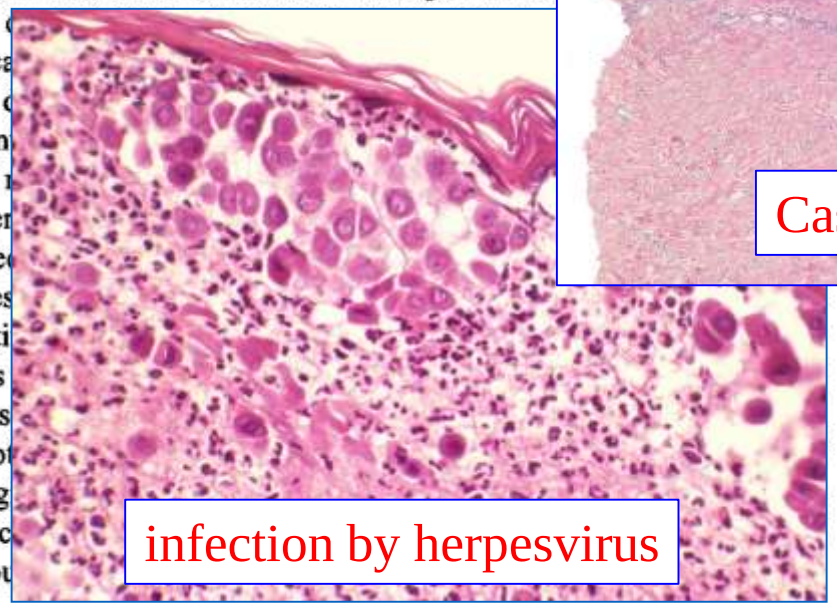

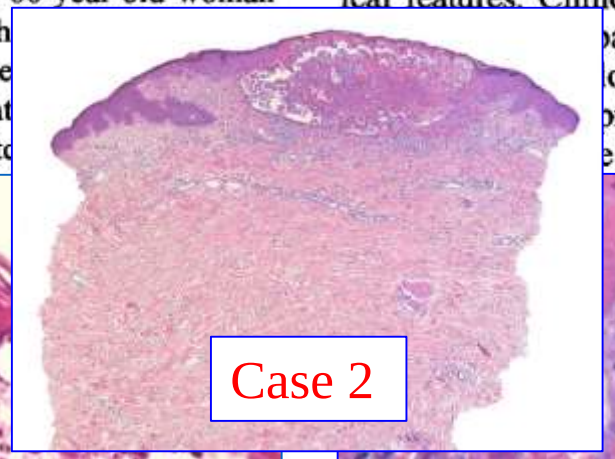

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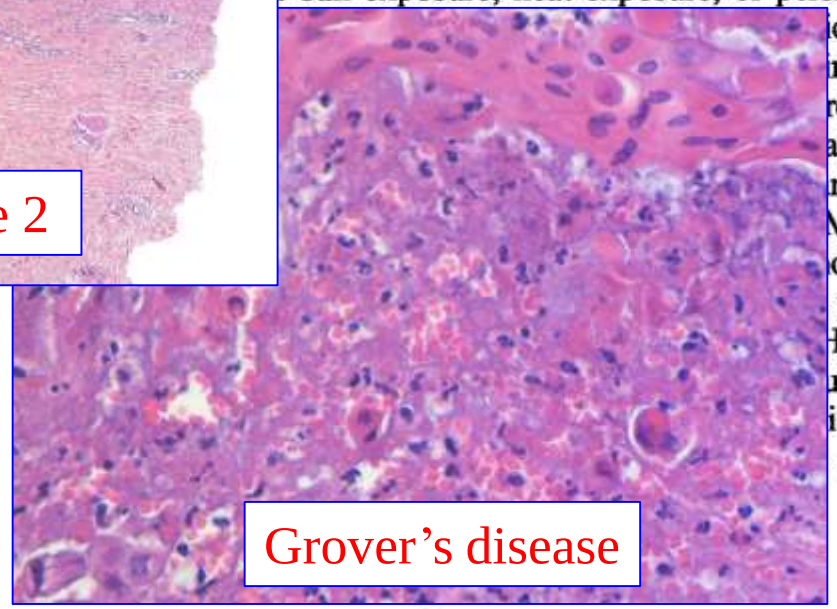

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as in our case 2 that came under the clinical diagnosis of dermatitis herpetiformis. In brief, as in biology at large,

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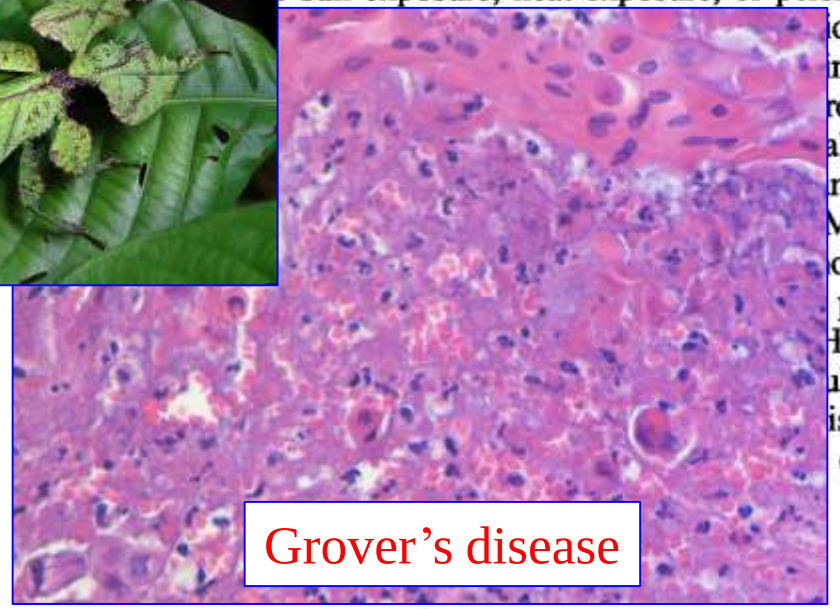

Grover's disease

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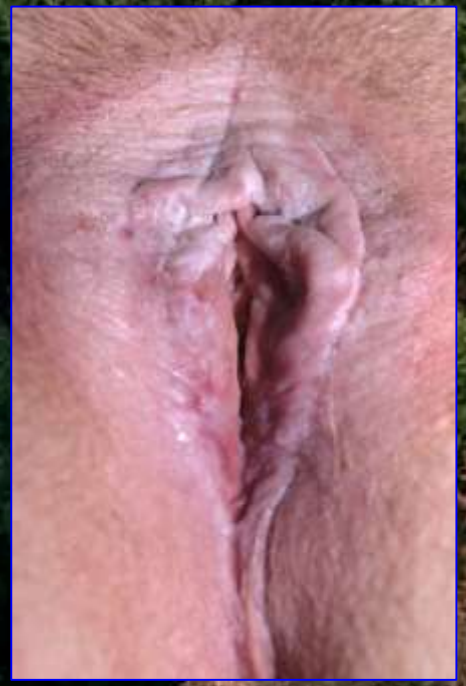
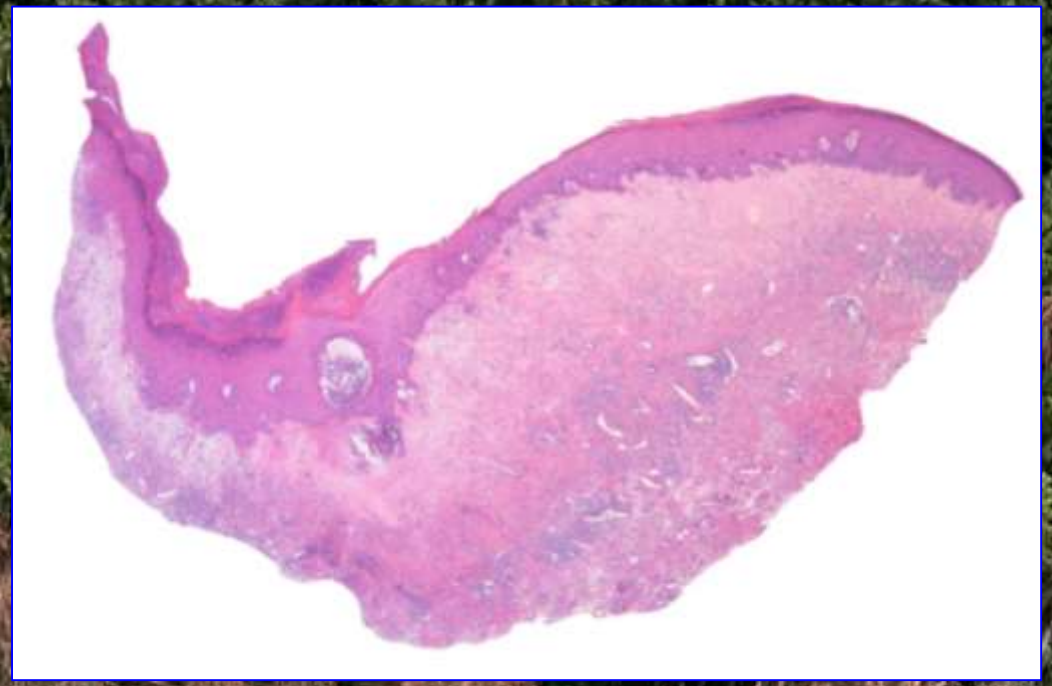
one species may mimick another.

Difficulties in the classification of individual cases of a disease may be caused by a variety of problems.

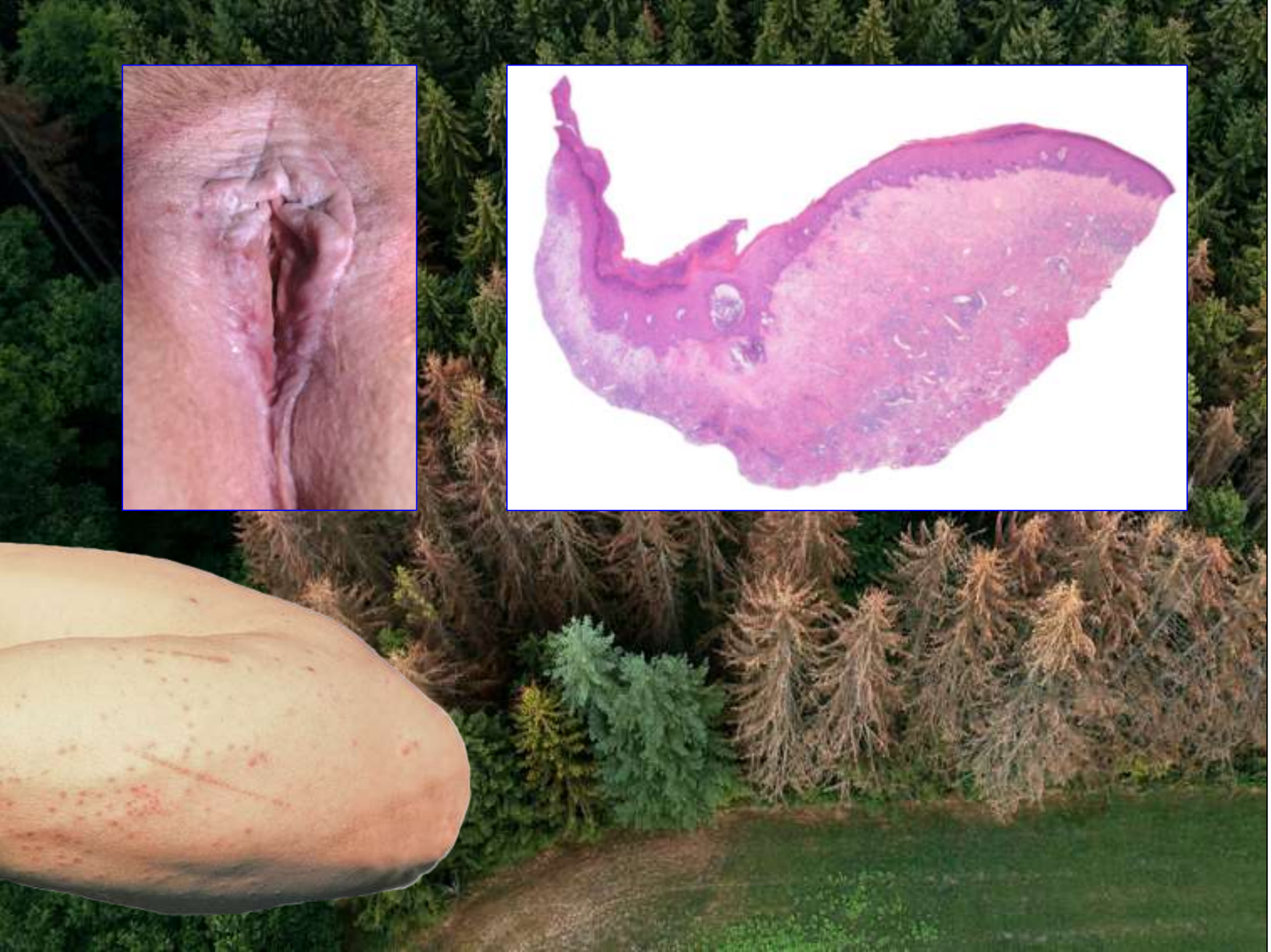
For one, the presentation of diseases, just like that of plants and animals, may vary strikingly in dependance from the stage of development and the predisposition of the individual.

Moreover, in all fields of biology, the presentation may be modified by external influences, such as a drought affecting trees,

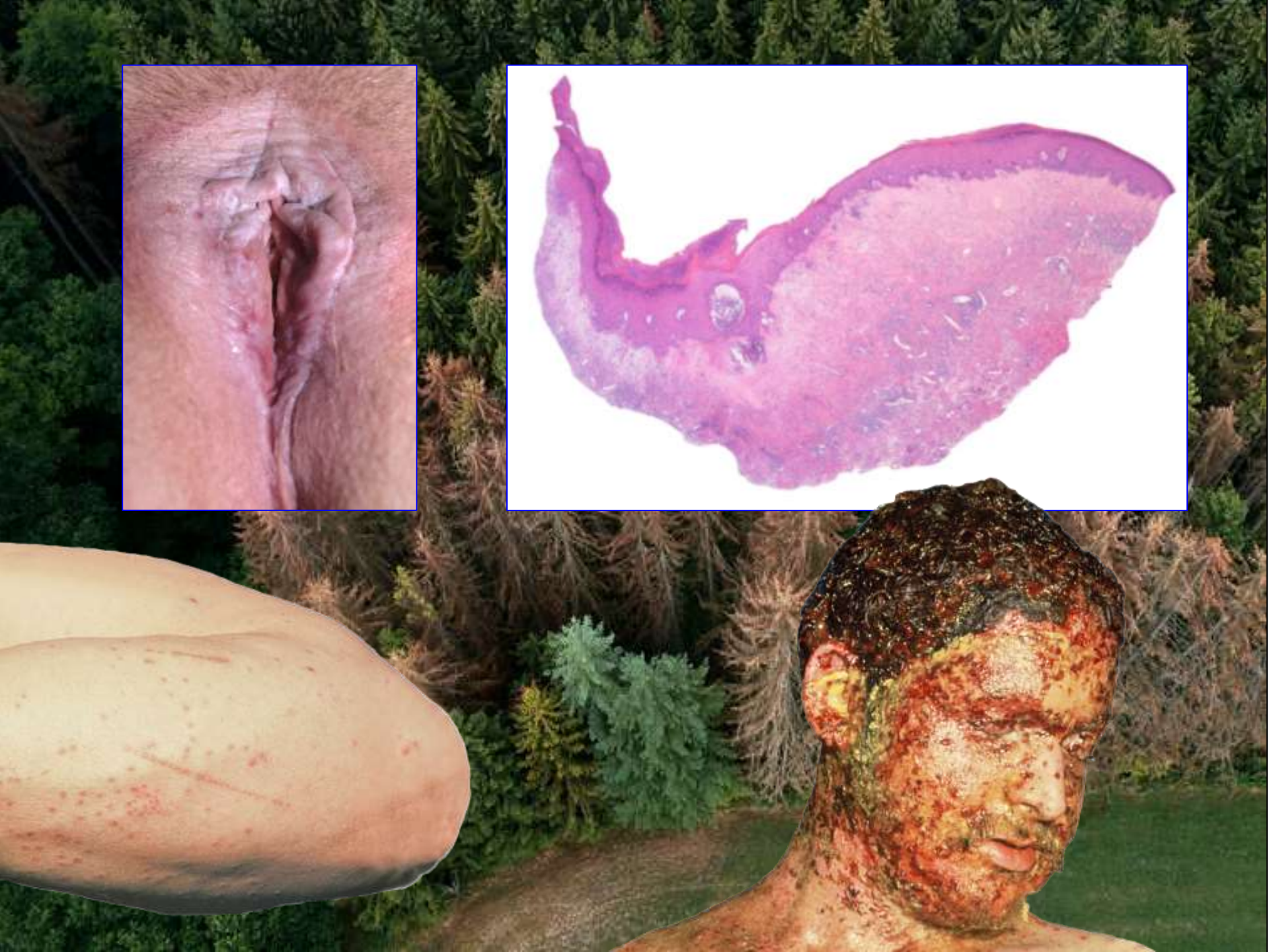




or, in the case of skin diseases, a finger that rubs or scratches so that lichen simplex chronicus becomes superimposed on other conditions, such as lichen sclerosus. In the case of diseases, the situation is complicated further by the fact that inflammation may contribute to their manifestation,

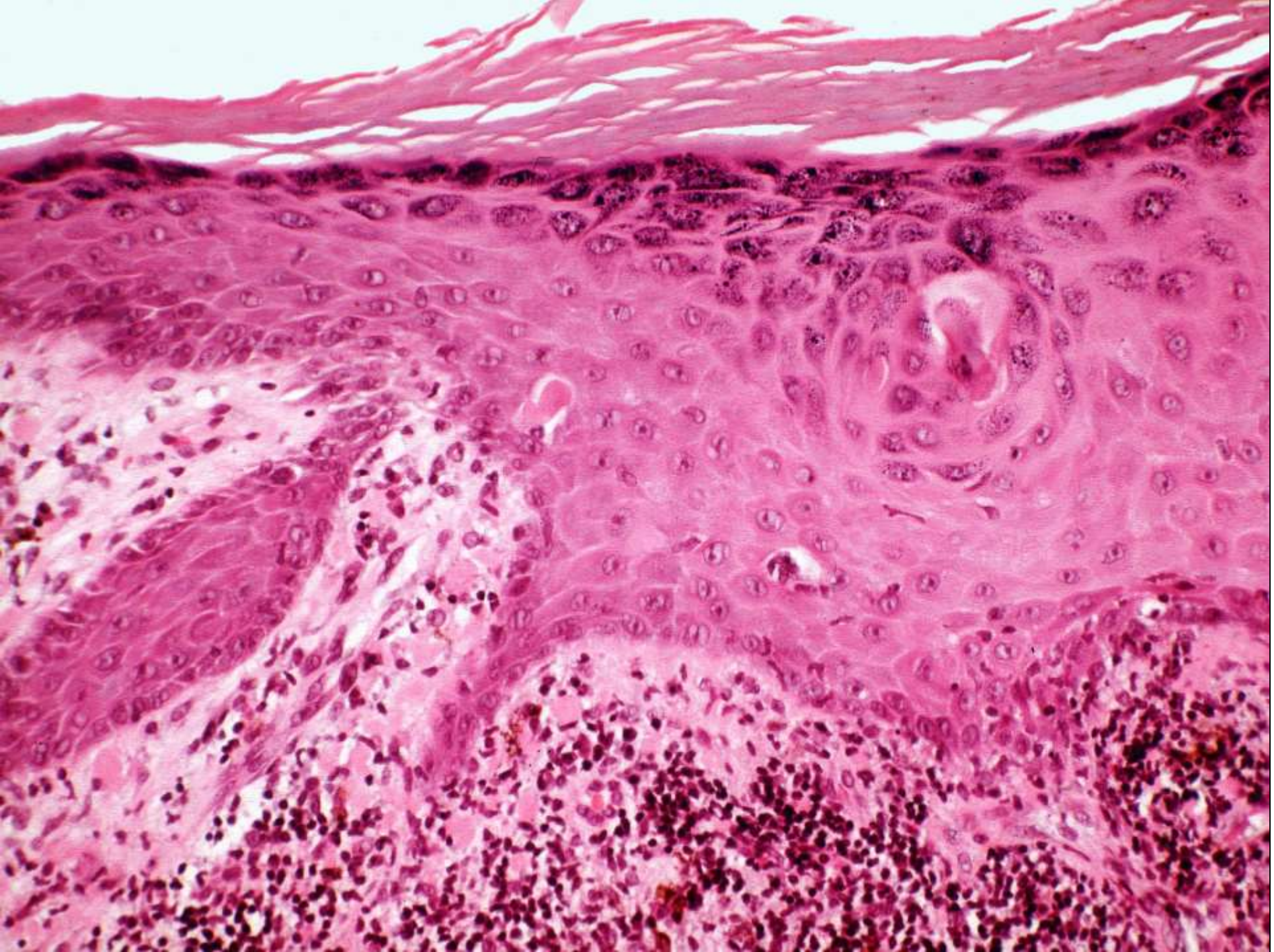


one process eliciting the other through the “Koebner phenomenon,” as in psoriasis or lichen planus.

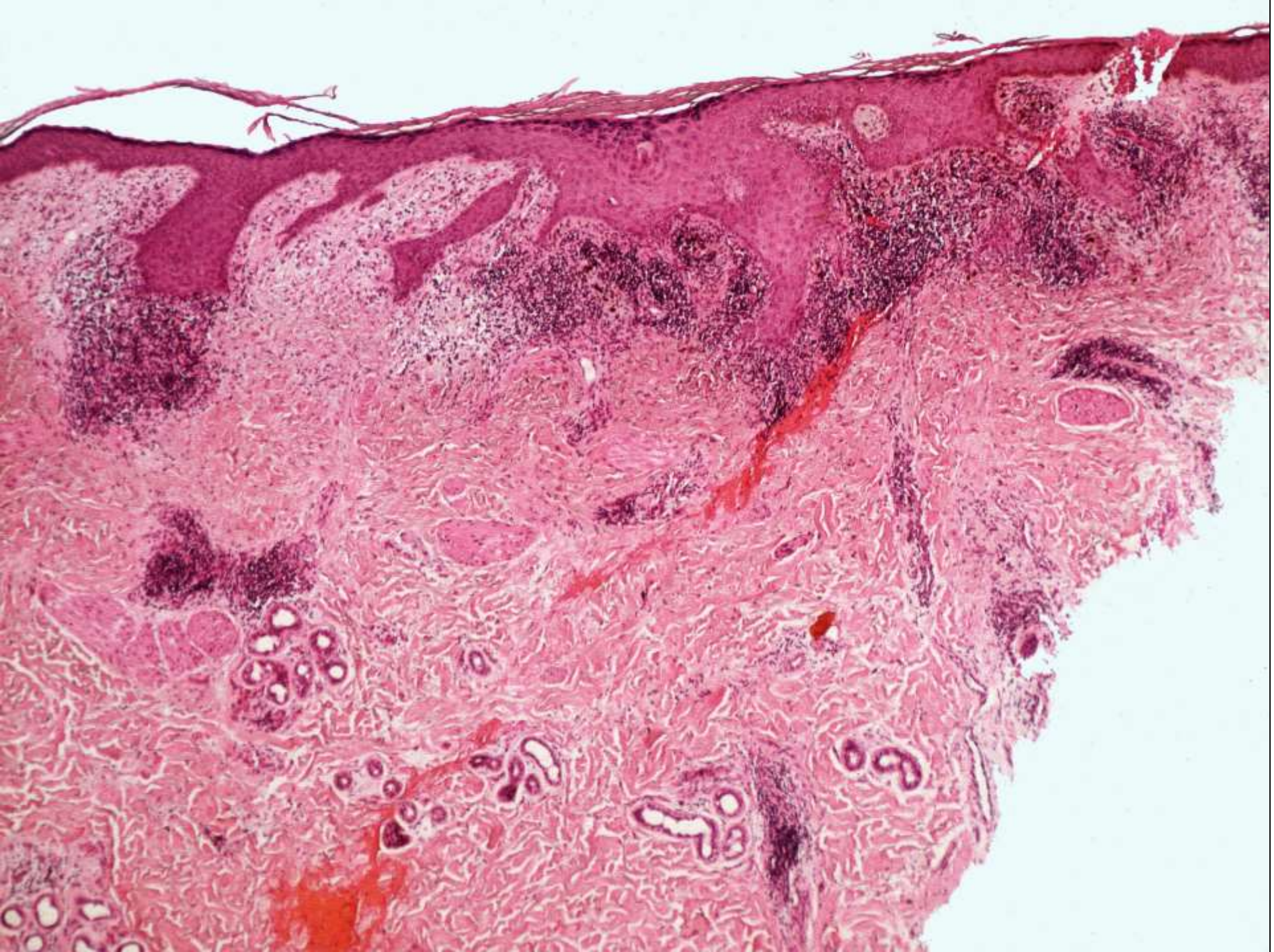


Some diseases may predispose to the development of others, such as immunodeficiencies to the development of various infectious diseases. And, of course, diseases may be associated just by chance.

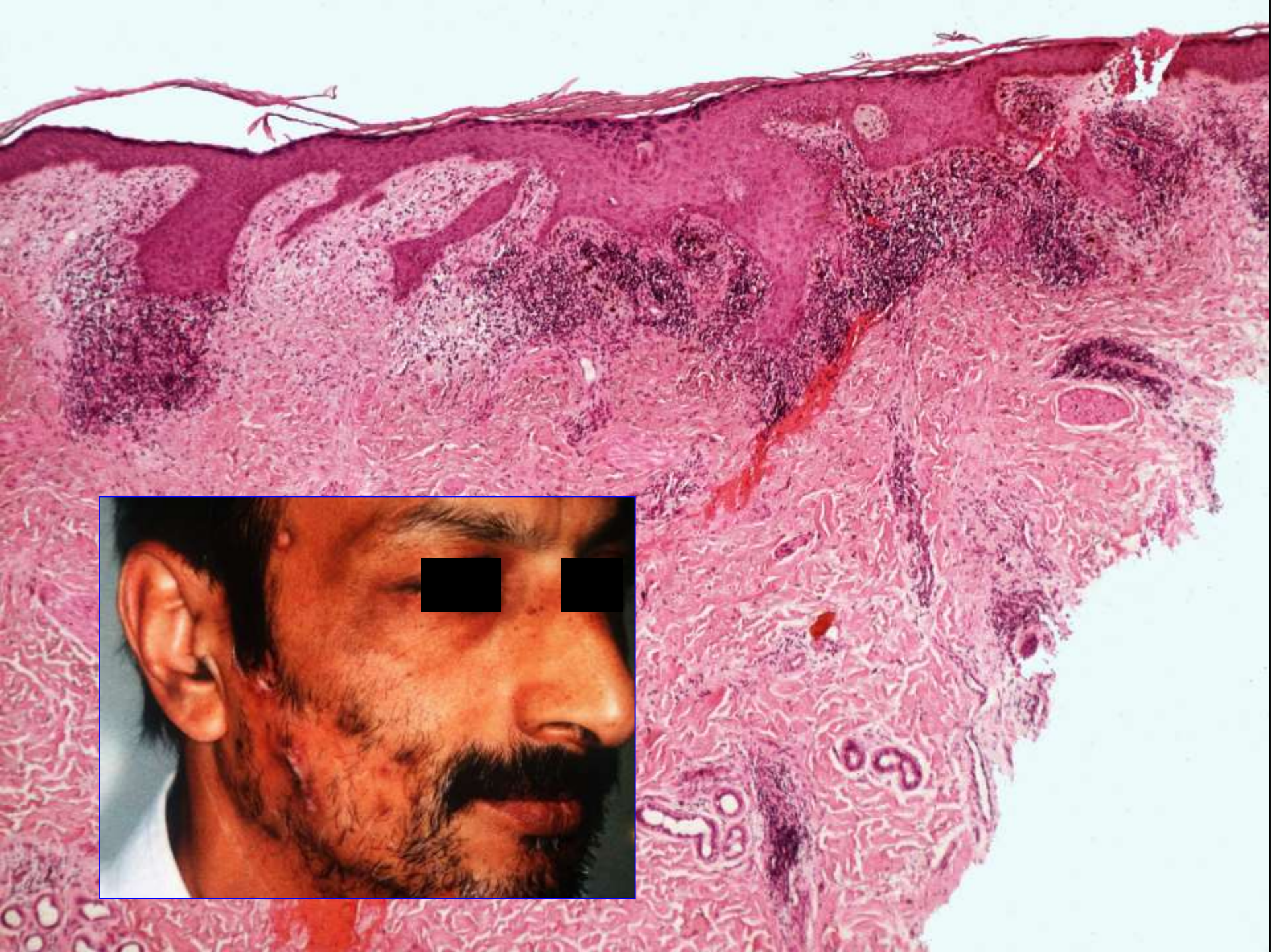
In brief, although inflammatory skin diseases have become accepted as distinct biologic entites, and can generally be recognized with specificity, there are always cases that are unusual and defy clearcut categorization. Often the dilemma can be resolved by integration of different findings.



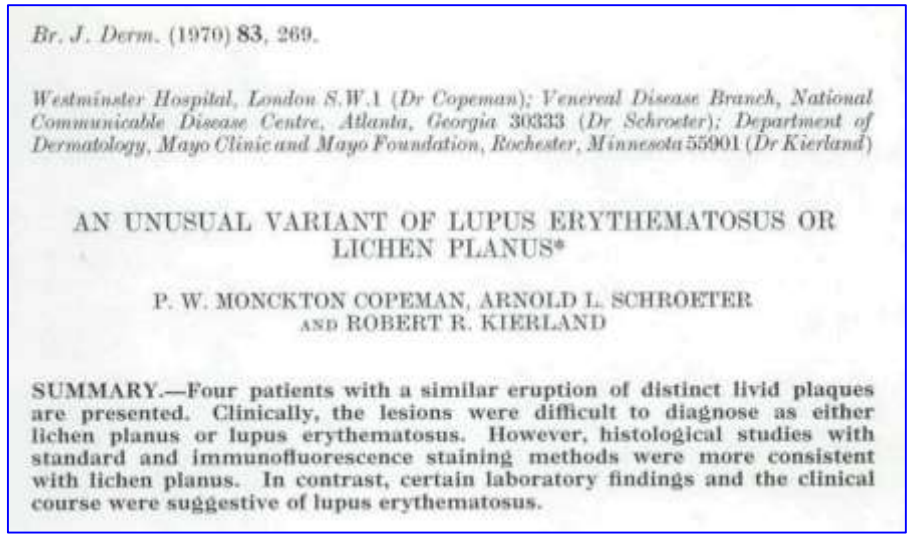
For example, these changes resemble lichen planus because of epithelial hyperplasia with wedge-shaped hypergranulosis and compact orthokeratosis, a “saw tooth pattern” of rete ridges, squamatisation of the basal cell layer, necrotic keratocytes, melanophages in the papillary dermis, and a dense, band-like infiltrate of lymphocytes that partially obscures the junction – all of which are criteria of lichen planus. However, the infiltrate is not dense throughout



and extends into the deep dermis which is highly unusual for lichen planus. This is, in fact, hypertrophic lupus erythematosus,



and the clinical picture is typical of LE. Sometimes, however, clinical differentiation of both diseases may also cause problems, and such cases



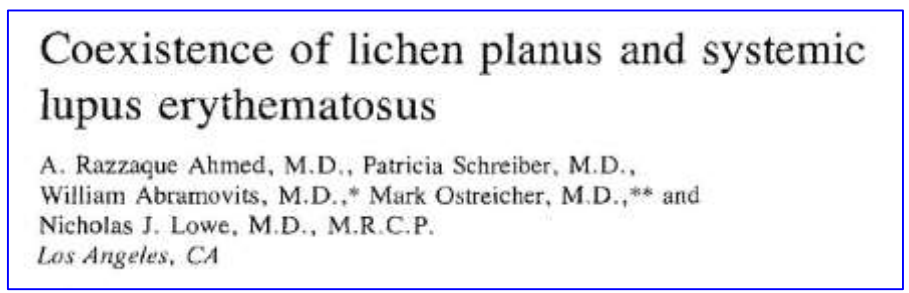
Br. J. Derm. (1970) **83**, 269.

Westminster Hospital, London S.W.1 (Dr Copeman); Venereal Disease Branch, National Communicable Disease Centre, Atlanta, Georgia 30333 *(Dr Schroeter); Department of Dermatology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota* 55901 *(Dr Kierland)*

AN UNUSUAL VARIANT OF LUPUS ERYTHEMATOSUS OR LICHEN PLANUS*

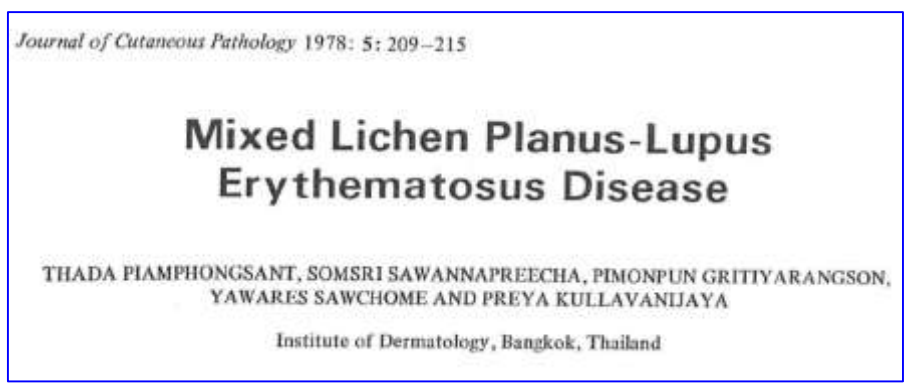
P. W. MONCKTON COPEMAN, ARNOLD L. SCHROETER AND ROBERT R. KIERLAND

SUMMARY.—Four patients with a similar eruption of distinct livid plaques are presented. Clinically, the lesions were difficult to diagnose as either lichen planus or lupus erythematosus. However, histological studies with standard and immunofluorescence staining methods were more consistent with lichen planus. In contrast, certain laboratory findings and the clinical course were suggestive of lupus erythematosus.



Coexistence of lichen planus and systemic lupus erythematosus

A. Razzaque Ahmed, M.D., Patricia Schreiber, M.D., William Abramovits, M.D.,* Mark Ostreicher, M.D.,** and Nicholas J. Lowe, M.D., M.R.C.P.
Los Angeles, CA



Journal of Cutaneous Pathology 1978: 5: 209–215

Mixed Lichen Planus-Lupus Erythematosus Disease

THADA PIAMPHONGSANT, SOMSRI SAWANNAPREECHA, PIMONPUN GRITIYARANGSON, YAWARES SAWCHOME AND PREYA KULLAVANIJAYA

Institute of Dermatology, Bangkok, Thailand

Hautarzt
1998 · 49:295–302 © Springer-Verlag 1998

Originalien

Vera Mahler · Otto Paul Hornstein · Sabine Meyer · Hans-Peter Albrecht
Franklin Kiesewetter · Dermatologische Universitätsklinik Erlangen (Direktor: Prof. Dr. G. Schuler)

Lupus-erythematodes-/Lichen-ruber-planus-Overlap-Syndrom

5 Fälle im Patientengut der Dermatologischen Universitätsklinik Erlangen (1984–1995)

Zusammenfassung

Das simultane Vorkommen von Lupus-erythematodes-(LE-) und Lichen-ruber-planus-(LP-) artigen Symptomen wird als LE/LP-Overlap-Syndrom (LE/LP-OS) bezeichnet. Es wird definiert durch das gleichzeitige Vorkommen klinischer, histologischer und immunhistologischer Charakteristika beider Krankheitsbilder. In der Literatur sind bisher 47 Patienten mit dieser seltenen Erkrankung beschrieben, wobei die klinischen Erscheinungsbilder heterogen sind: Die einzelnen Hauterscheinungen zeigen ein zwischen LE und LP intermediäres Erscheinungsbild (Typ I=intermediärer Typ) oder aber ein Nebeneinander von LE- und LP-typischen Efflorescenzen (Typ II=polarer Typ). Zur Bestimmung der Häufigkeit und Charakteristika des LE/LP-OS untersuchten wir retrospektiv unser LE-Patientengut von 1984–1995: In 5 Fällen wurde die Diagnose eines LE/LP-OS gestellt. Das LE/LP-OS ist demnach im untersuchten Kollektiv häufiger als bisher angenommen. Aufgrund der großen Variationsbreite der klinischen, histologischen und immunhistologischen Befunde und Fehlen pathognomonischer Merkmale des LE/LP-OS, wird die Diagnose möglicherweise zu selten gestellt. Da sich jedoch aus der Diagnose therapeutische Konsequenzen ergeben, werden Kriterien vorgestellt, die Erkennen und Abgrenzung des LE/LP-OS erleichtern.

Schlüsselwörter

Lupus-erythematodes-/Lichen-ruber-Overlap-Syndrom · Intermediärer Typ · Polarer Typ · Punktesystem

Das Lupus-erythematodes-/Lichen-ruber-planus-Overlap-Syndrom (LE/LP-OS) wird definiert durch das gleichzeitige Vorkommen klinischer, histologischer und immunhistologischer Merkmale beider Krankheitsbilder [2, 18]. Die Zuordnung zu nur einer der beiden Dermatosen ist klinisch nicht sicher möglich. Basierend auf den bisherigen Arbeiten in der Literatur, variieren die histologischen Veränderungen in unterschiedlichem Ausmaß von LE zu LP, sind aber meist eher mit LP vereinbar. Die Laborparameter (i.e. antinukleäre Antikörper) weisen häufig auf einen LE hin.

Copeman et al. beschrieben 1970 erstmals 4 Fälle simultanen Vorkommens von LE- und LP-artigen Hautveränderungen bzw. Organsymptomen [4]. Das LE/LP-OS subsumiert sowohl Überlappungen von Lichen ruber mit typischen Symptomen von discoidem LE, als auch von systemischem LE [1, 4] (s. Tabelle 1). Zwischenzeitlich sind 43 weitere Fälle dieses seltenen Overlap-Syndroms beschrieben [18].

Mit der vorliegenden retrospektiven Studie wurde die Häufigkeit des LE/LP-OS in unserem Patientengut der Jahre 1984–1995 ermittelt. Die Wertigkeit der klinischen Charakteristika wurde bestimmt. Unter Einbeziehung der in der Literatur beschriebenen 47 Fälle wurden Kriterien erarbeitet, die die Diagnosestellung dieses seltenen Krankheitsbildes erleichtern.

Materialien und Methoden

Im Rahmen der Retrospektivstudie wurden alle Patientenakten von 1984 bis einschließlich 1995 gesichtet, bei denen die Abklärung der Verdachtsdiagnose eines LE zur stationären Aufnahme an der Dermatologischen Universitätsklinik Erlangen führte. 5 der untersuchten 166 Fällen wiesen chronische Hauterscheinungen mit sowohl Lupus erythemathodes-, als auch Lichen-ruber-planus-typischen Merkmalen auf.

In allen Fällen war Fotodokumentation und labormedizinische Abklärung zum Ausschluß eines systemischen LE erfolgt (BKS, RF, ANA, Antikörper-Profil – i.e. Antikörper gegen Ro, La, RNP/Sm, Sm, dsDNS-, Komplement C_3, C_4). Mehrere Gewebeproben für Histologie und direkte Immunfluo-

Dr. V. Mahler
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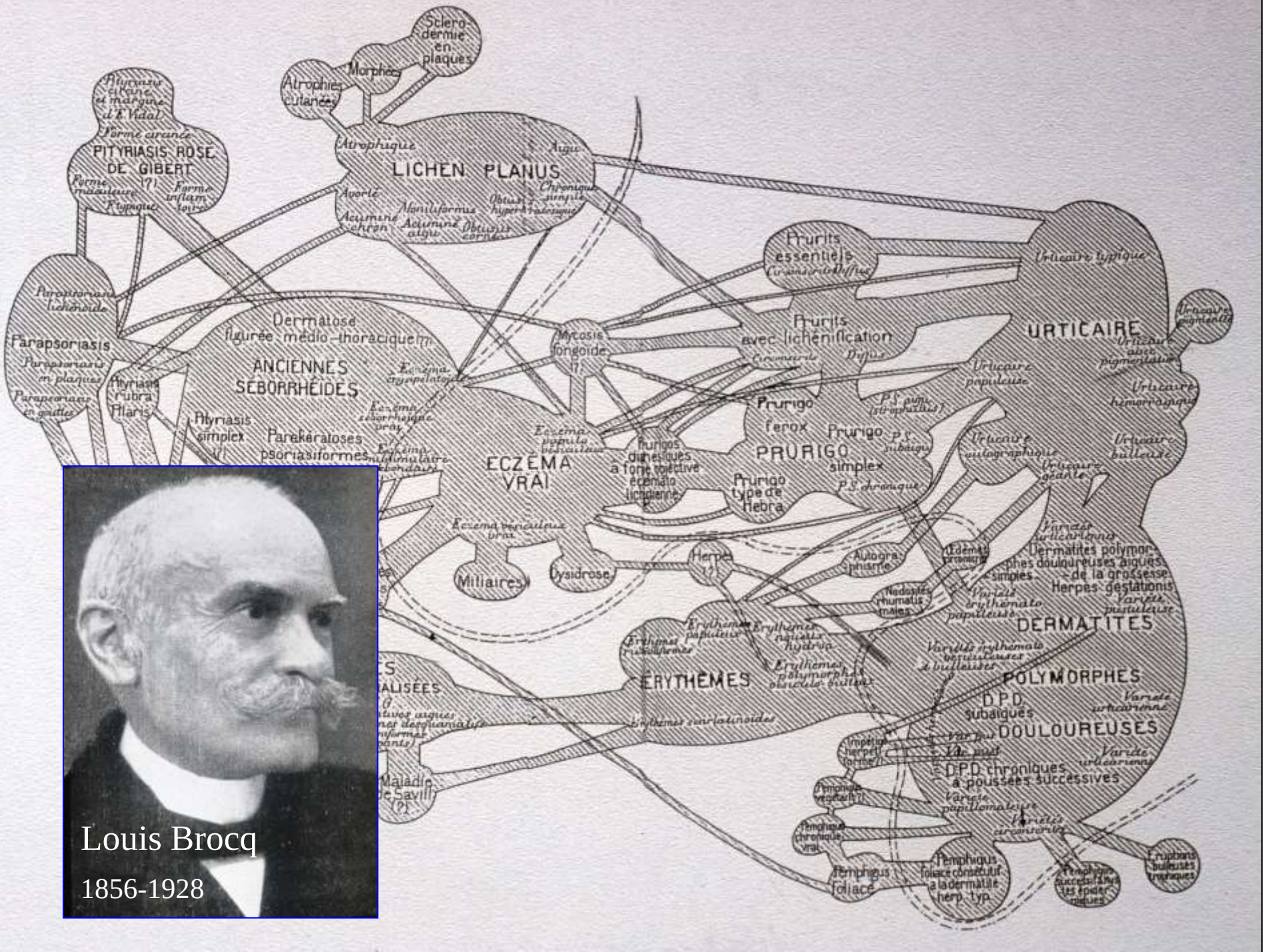
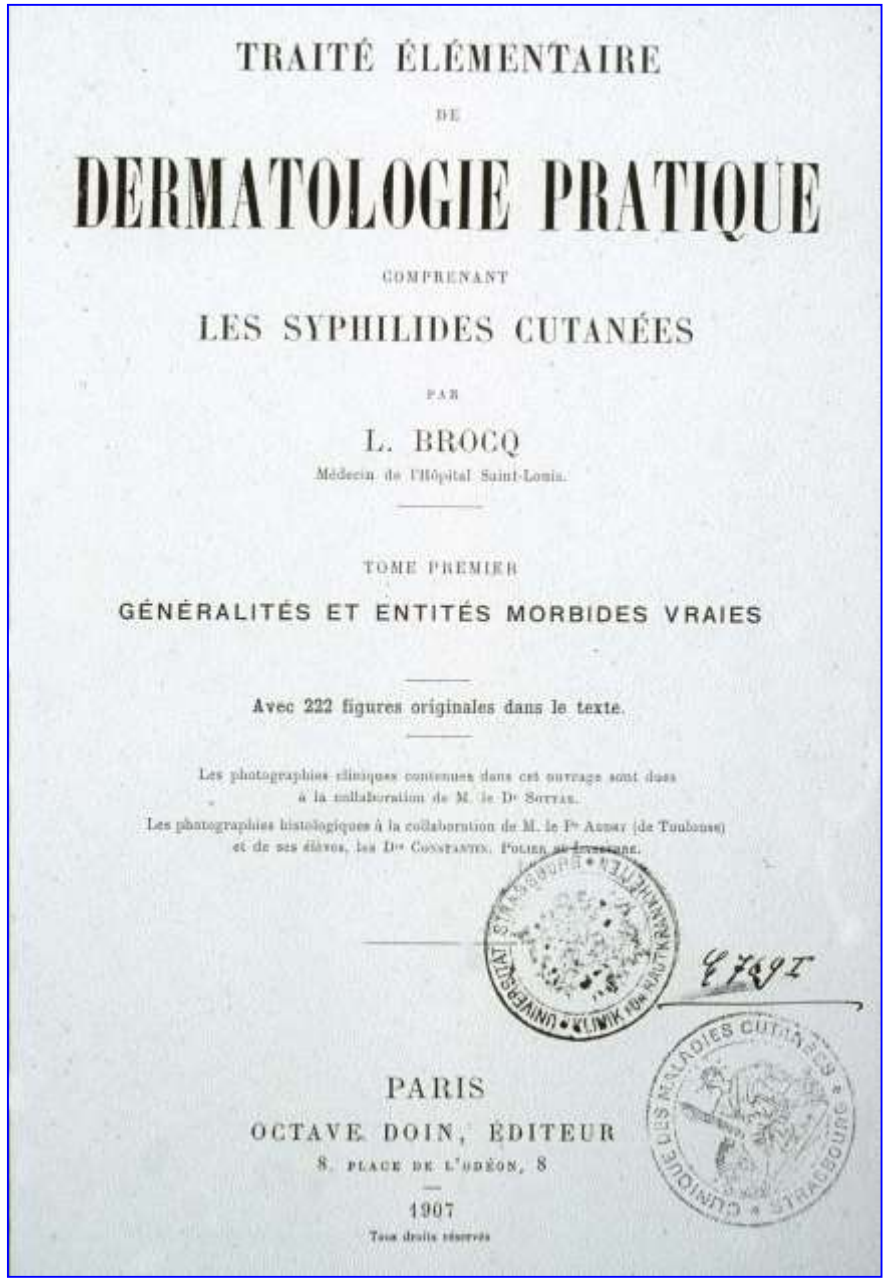
have been interpreted in different ways: as *"an unusual variant of lupus erythematosus or lichen planus,"* i.e., a problem of differential diagnosis, as the *"coexistence of lichen planus and … lupus erythematosus,"* i.e., as the development by chance of two diseases in the same patient, and, last, as *"mixed lichen planus-lupus erythematosus disease,"* i.e., a *"lupus-erythematosus/lichen-ruber-planus-overlap-syndrome,"*



Louis Brocq
1856-1928

strictly in the tradition of Brocq's "nebules of dermatoses."

One reason for this fall-back to obsolete concepts of the early 20th century is the unknown etiology of both diseases. This was the chief consideration of Brocq when he advanced his concept of "nebules of dermatoses."



TRAITÉ ÉLÉMENTAIRE

DE

DERMATOLOGIE PRATIQUE

COMPRENANT

LES SYPHILIDES CUTANÉES

PAR

L. BROCQ

Médecin de l'Hôpital Saint-Louis.

TOME PREMIER

GÉNÉRALITÉS ET ENTITÉS MORBIDES VRAIES

Avec 222 figures originales dans le texte.

Les photographies cliniques contenues dans cet ouvrage sont dues à la collaboration de M. le Dr Sottas.

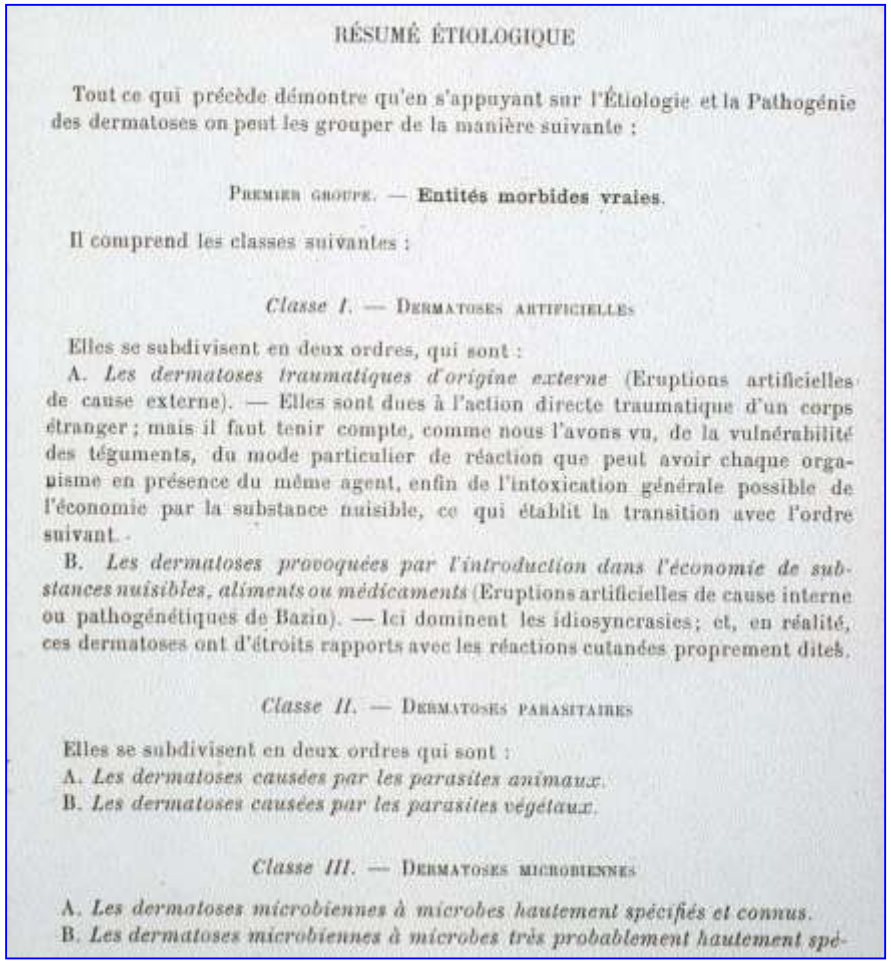
Les photographies histologiques à la collaboration de M. le Pr Audry (de Toulouse) et de ses élèves, les Drs Constantin, Polier de Lausanne.

PARIS

OCTAVE DOIN, ÉDITEUR

8, PLACE DE L'ODÉON, 8

1907



RÉSUMÉ ÉTIOLOGIQUE

Tout ce qui précède démontre qu'en s'appuyant sur l'Étiologie et la Pathogénie des dermatoses on peut les grouper de la manière suivante :

Premier groupe. — **Entités morbides vraies.**

Il comprend les classes suivantes :

Classe I. — Dermatoses artificielles

Elles se subdivisent en deux ordres, qui sont :

A. *Les dermatoses traumatiques d'origine externe* (Eruptions artificielles de cause externe). — Elles sont dues à l'action directe traumatique d'un corps étranger ; mais il faut tenir compte, comme nous l'avons vu, de la vulnérabilité des téguments, du mode particulier de réaction que peut avoir chaque organisme en présence du même agent, enfin de l'intoxication générale possible de l'économie par la substance nuisible, ce qui établit la transition avec l'ordre suivant.

B. *Les dermatoses provoquées par l'introduction dans l'économie de substances nuisibles, aliments ou médicaments* (Eruptions artificielles de cause interne ou pathogénétiques de Bazin). — Ici dominent les idiosyncrasies ; et, en réalité, ces dermatoses ont d'étroits rapports avec les réactions cutanées proprement dites.

Classe II. — Dermatoses parasitaires

Elles se subdivisent en deux ordres qui sont :

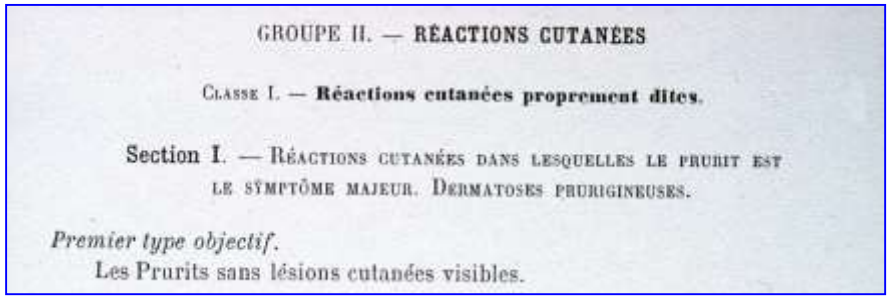
A. *Les dermatoses causées par les parasites animaux.*

B. *Les dermatoses causées par les parasites végétaux.*

Classe III. — Dermatoses microbiennes

A. *Les dermatoses microbiennes à microbes hautement spécifiés et connus.*

B. *Les dermatoses microbiennes à microbes très probablement hautement spé-*



GROUPE II. — **RÉACTIONS CUTANÉES**

Classe I. — **Réactions cutanées proprement dites.**

Section I. — Réactions cutanées dans lesquelles le prurit est le symptôme majeur. Dermatoses prurigineuses.

Premier type objectif.

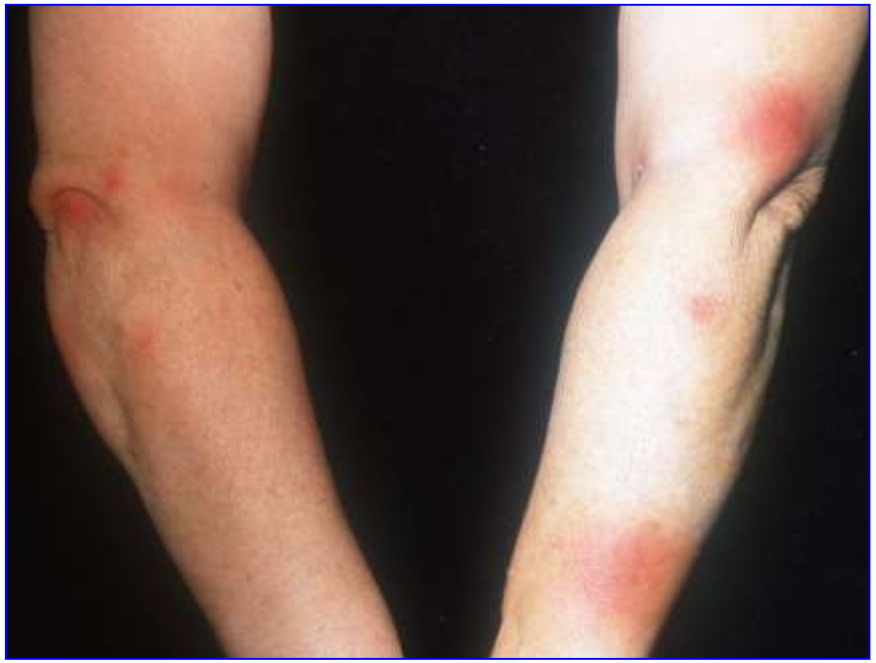
Les Prurits sans lésions cutanées visibles.

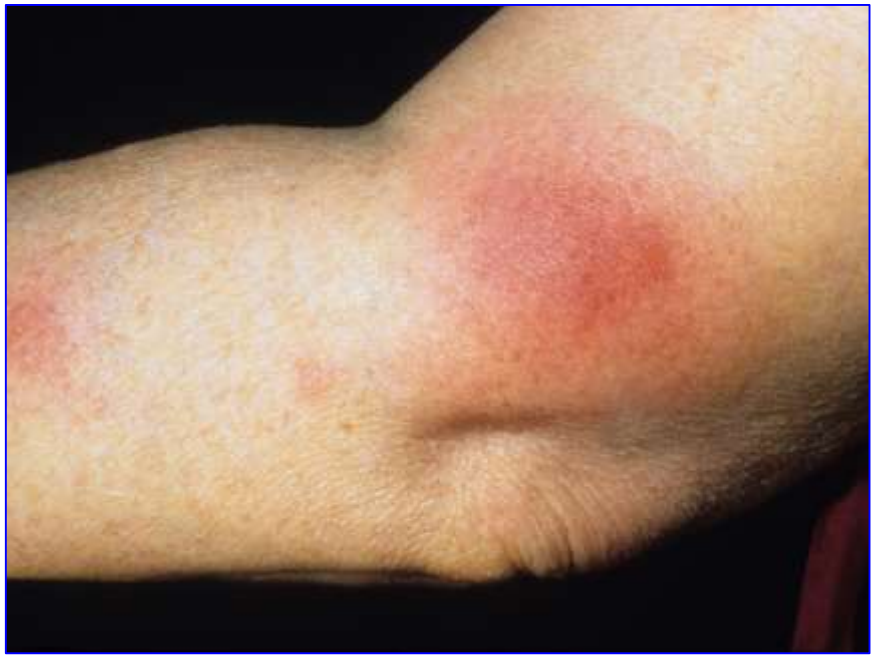
In his textbook of 1907, he accepted as true disease entities, "*entités morbides vraies,*" only those with a clearly established etiology, namely, artificial, parasitic, and microbial dermatoses. All others were interpreted as non-specific reaction patterns, *"réactions cutanées."* This attitude has survived,

I have come to think of skin diseases more as patterns than as authentic diseases, with the exception of some infectious diseases.

A. B. Ackerman, 2003

, and in 2003 even Bernard Ackerman noted: "*I have come to think of skin diseases more as patterns than as authentic diseases, with the exception of some infectious diseases.*" As 100 years before in the case of Brocq, this stance resulted from a perspective too narrow. Brocq focused on clinical aspects alone, Ackerman on histopathologic ones. A narrow focus may suffice for the identification of diseases, and may even facilitate it, but it is inadequate for their definition.





Pathophysiology and Histopathology

Erythema nodosum is a nonspecific cutaneous reaction pattern to a variety of antigens, with many immune-mediated mechanisms implicated. Most direct and indirect evidence supports the involvement of a type IV delayed hypersensitivity response to numerous antigens. Erythema nodosum often occurs in association with granulomatous disease, including sarcoidosis, tuberculosis, and granulomatous colitis.

stellate cleft—are a characteristic finding.[6] Erythema nodosum is not associated with vasculitis, although small vessel inflammation and hemorrhage can occur.

Causes of Erythema Nodosum

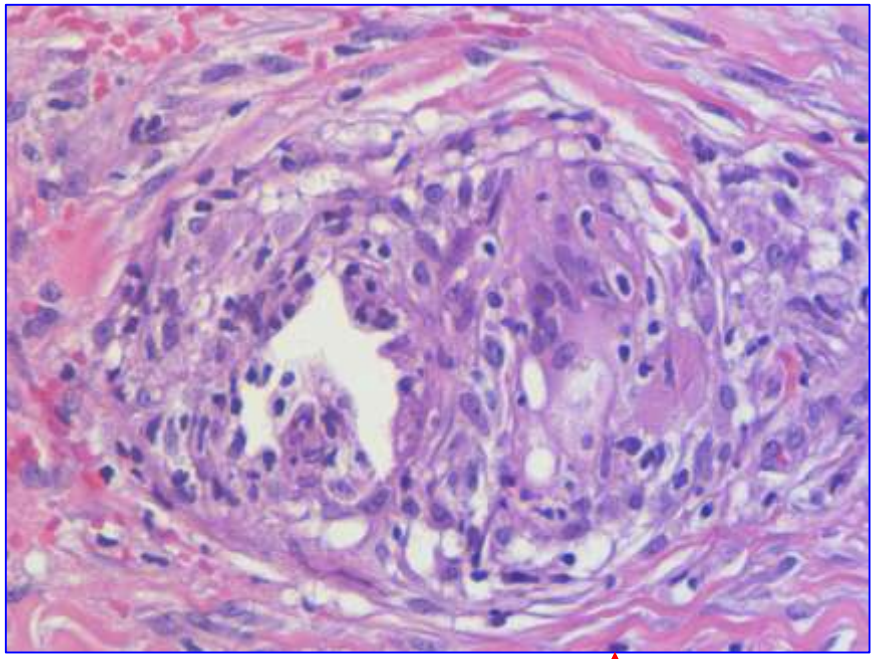
Erythema nodosum usually is idiopathic,[2,6,7] but there are many possible causes (*Table 2*). Physicians should consider all possible etiologies of erythema nodosum and take a comprehensive history. A summary of the steps for

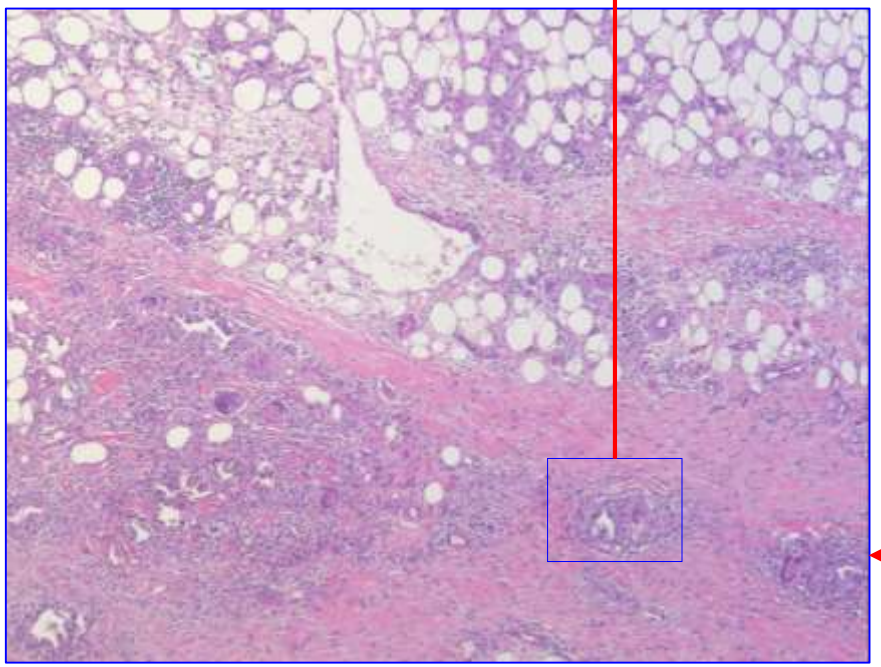
TABLE 2

Causes of Erythema Nodosum

Common
Idiopathic (up to 55 percent)
Infections: streptococcal pharyngitis (28 to 48 percent), *Yersinia* spp. (in Europe), mycoplasma, chlamydia, histoplasmosis, coccidioidomycosis, mycobacteria
Sarcoidosis (11 to 25 percent) with bilateral hilar adenopathy
Drugs (3 to 10 percent): antibiotics (e.g., sulfonamides, amoxicillin), oral contraceptives
Pregnancy (2 to 5 percent)
Enteropathies (1 to 4 percent): regional enteritis, ulcerative colitis
Rare (less than 1 percent)
Infections
Viral: herpes simplex virus, Epstein-Barr virus, hepatitis B and C viruses, human immunodeficiency virus
Bacterial: *Campylobacter* spp., rickettsiae, *Salmonella* spp., psittacosis, *Bartonella* spp., syphilis
Parasitic: amoebiasis, giardiasis
Miscellaneous: lymphoma, other malignancies

This includes the etiology which is also not decisive. Some diseases may be elicited by a wide variety of events, such as erythema nodosum which is often referred to as the prototype of a *“nonspecific cutaneous reaction pattern.”* However, despite the diversity of causes, erythema nodosum has a typical clinical presentation, i.e., development of a few, deep-seated, painful nodules chiefly at the extensor surfaces of the extremities, a typical age of onset, i.e., individuals in the third and fourth decade of life, a typical biologic course, i.e., remission usually within three to six weeks, irrespective of whether or not the eliciting cause persists,





Erythema Nodosum

Pathophysiology and Histopathology

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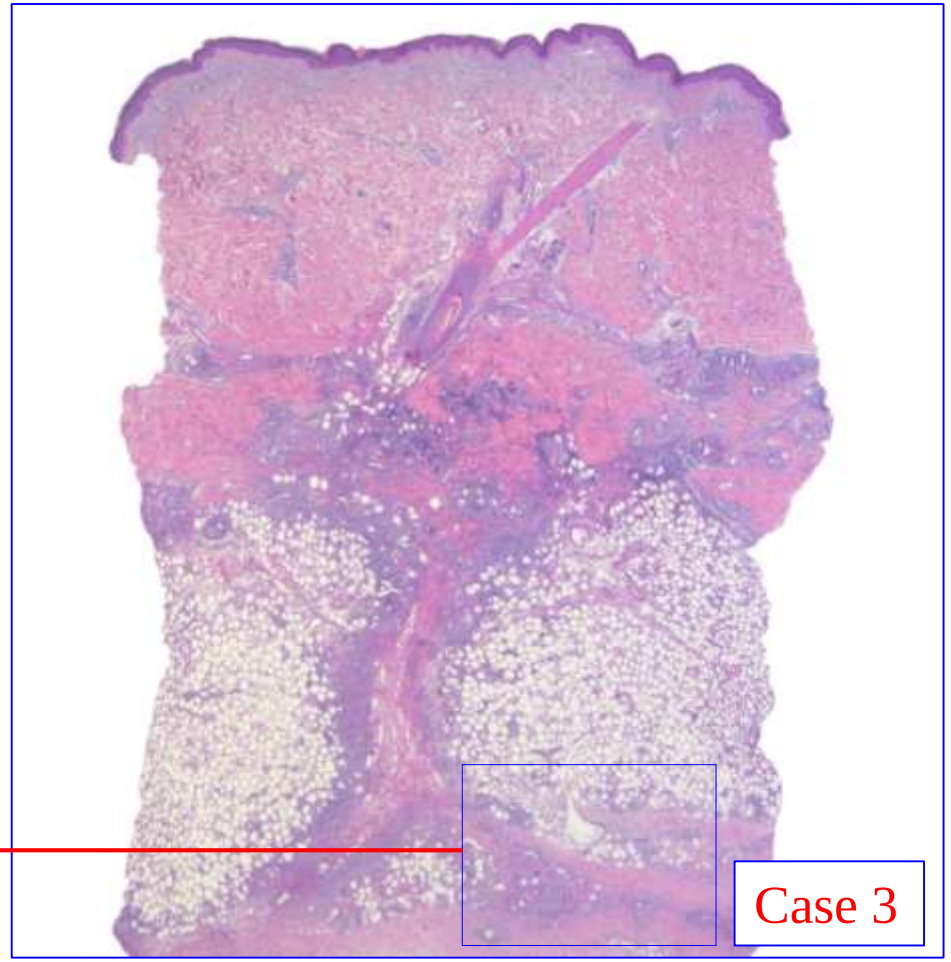
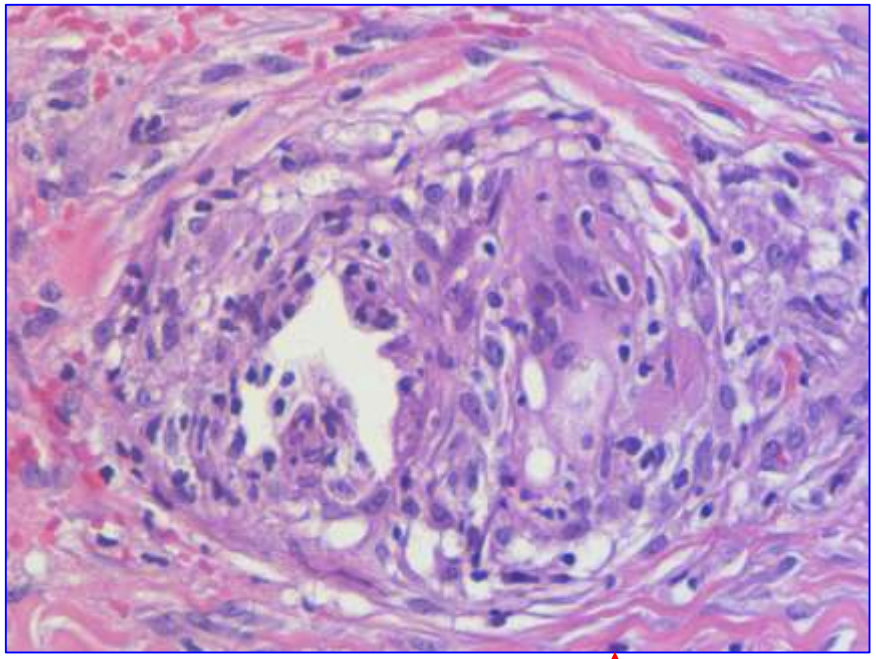
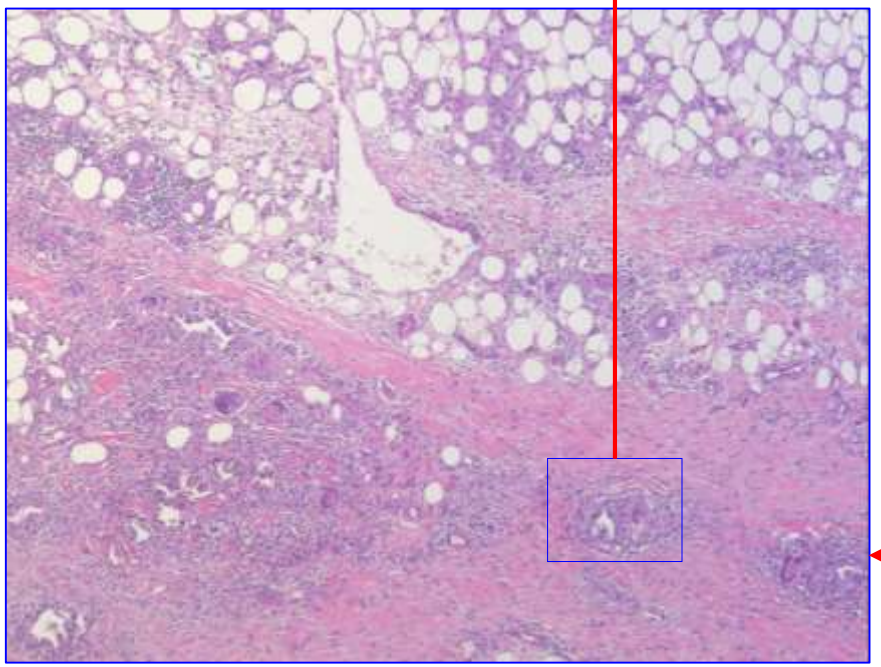


and typical histopathologic features, namely, a predominantly septal panniculitis without signs of vasculitis, marked thickening of the septa, a mixed inflammatory-cell infiltrate encroaching on the periphery of the lobules, and so-called Miescher's granulomas, i.e., small epithelioid cell granulomas which, typically, sport a cleft in their center, as seen in our case 3.



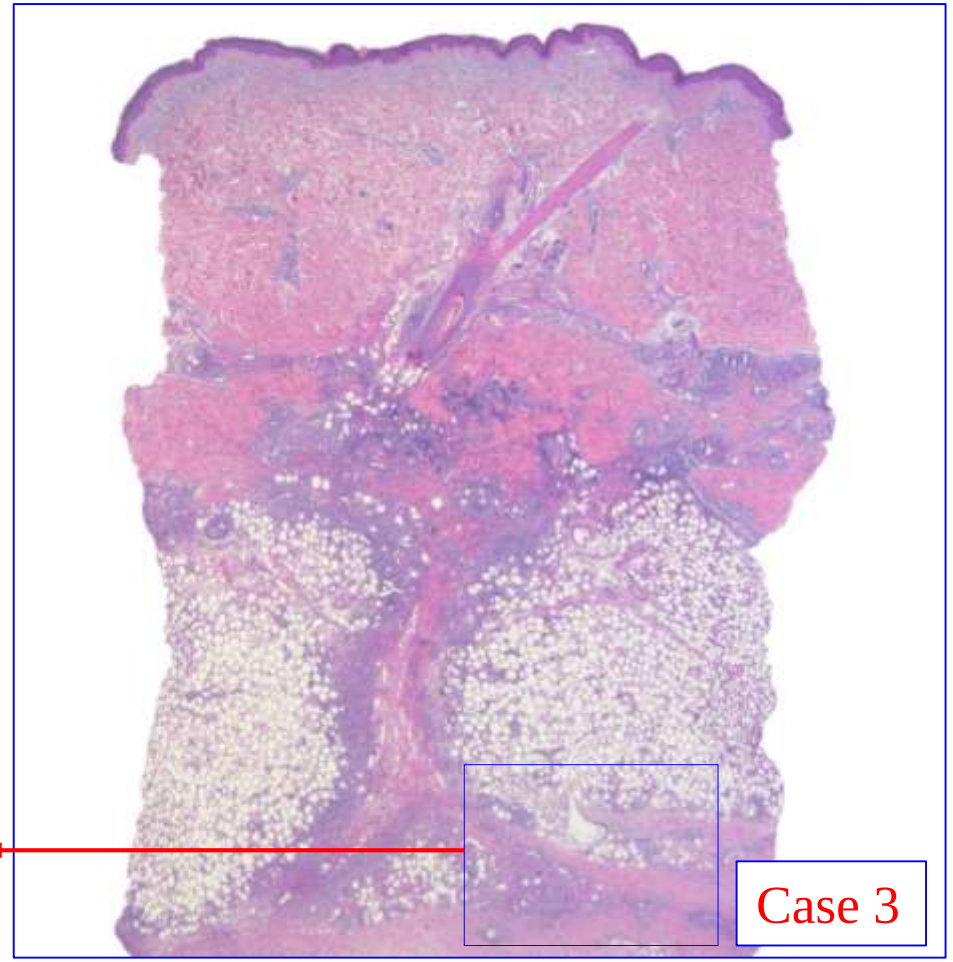


FAMILIAL ERYTHEMA NODOSUM

ORI ELKAYAM, DAN CASPI, RAFAEL SEGAL, CHAIM BRAUTBAR, ELDAD BEN-CHETRIT, and MICHAEL YARON

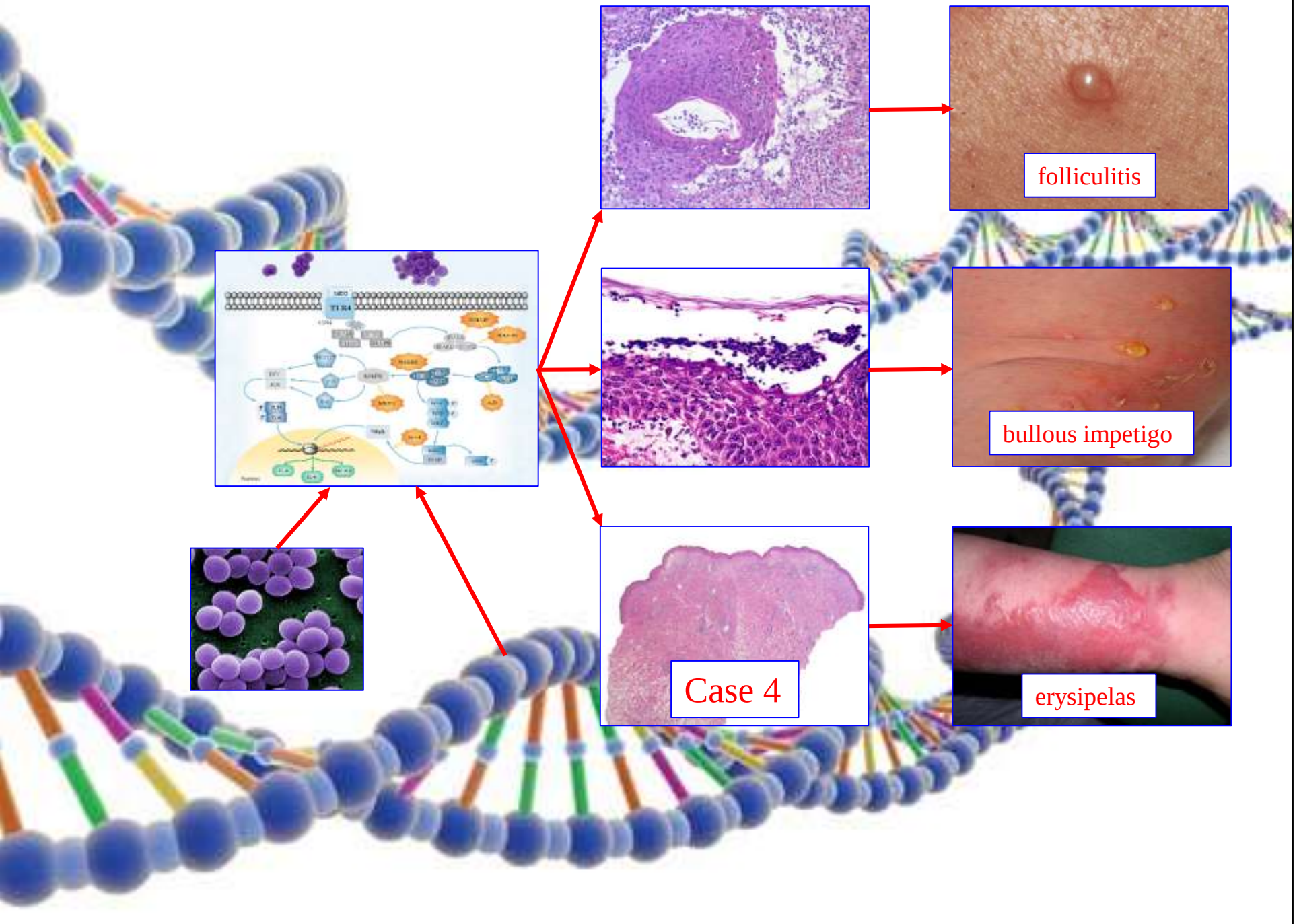
Erythema nodosum (EN) is a hypersensitivity reaction associated with many diseases. We describe a family in which 4 sisters had acute or recurrent EN. HLA typing showed a common haplotype in the affected members of the family. A review of familial EN and HLA distribution in EN is presented.

Case reports. Sister 1 (AP), 41 years old, was admitted to the hospital because of fever, painful lesions in both legs, and arthralgia of the ankles and knees. A month earlier she had had pharyngitis, which was treated with amoxicillin. On examination, her temperature was 38°C, and she had several raised, red,

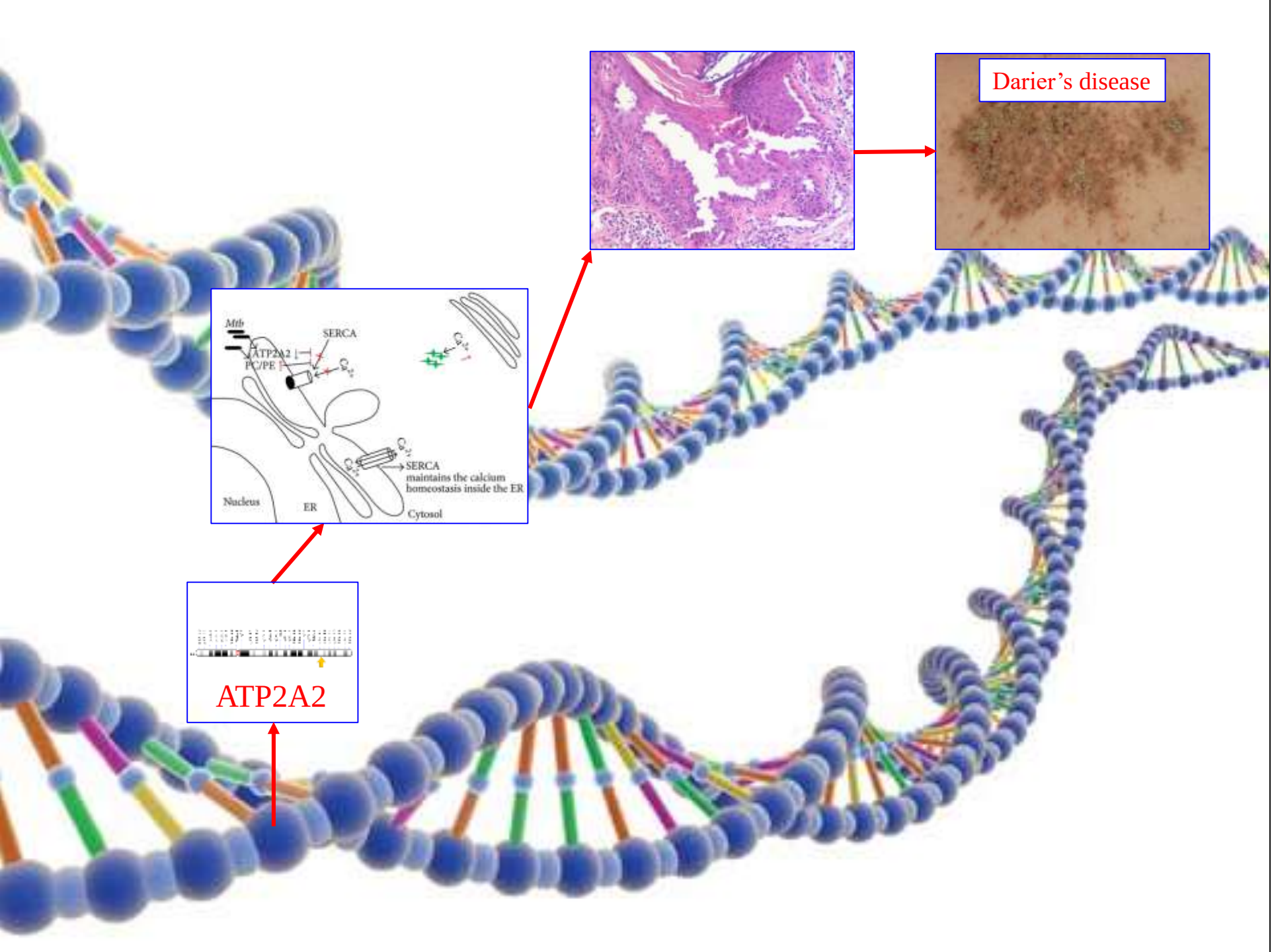


Case 3

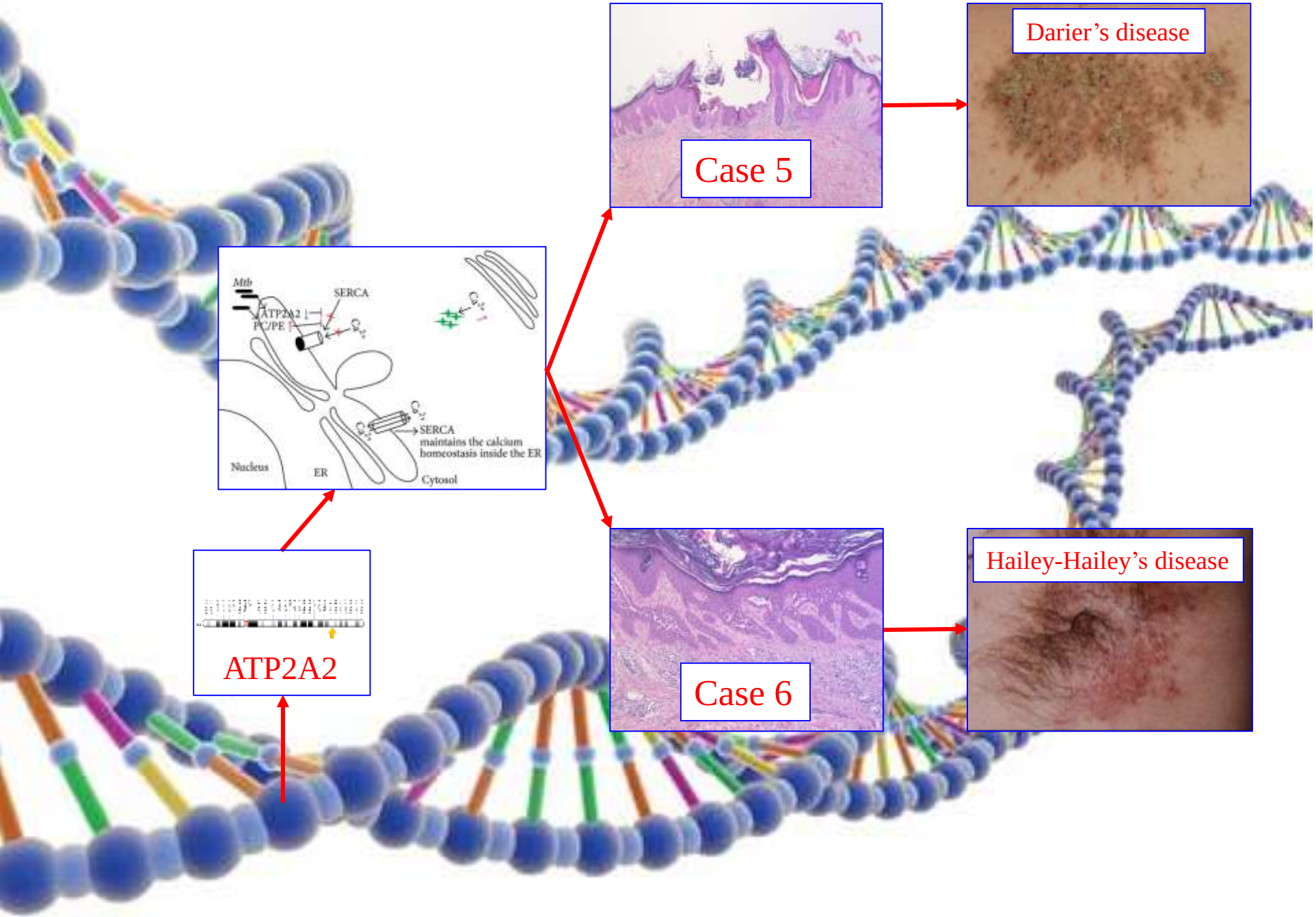
Moreover, familial cases of erythema nodosum have been described. Together, those correlated findings may qualify erythema nodosum as a specific disease, despite the diversity of causes.



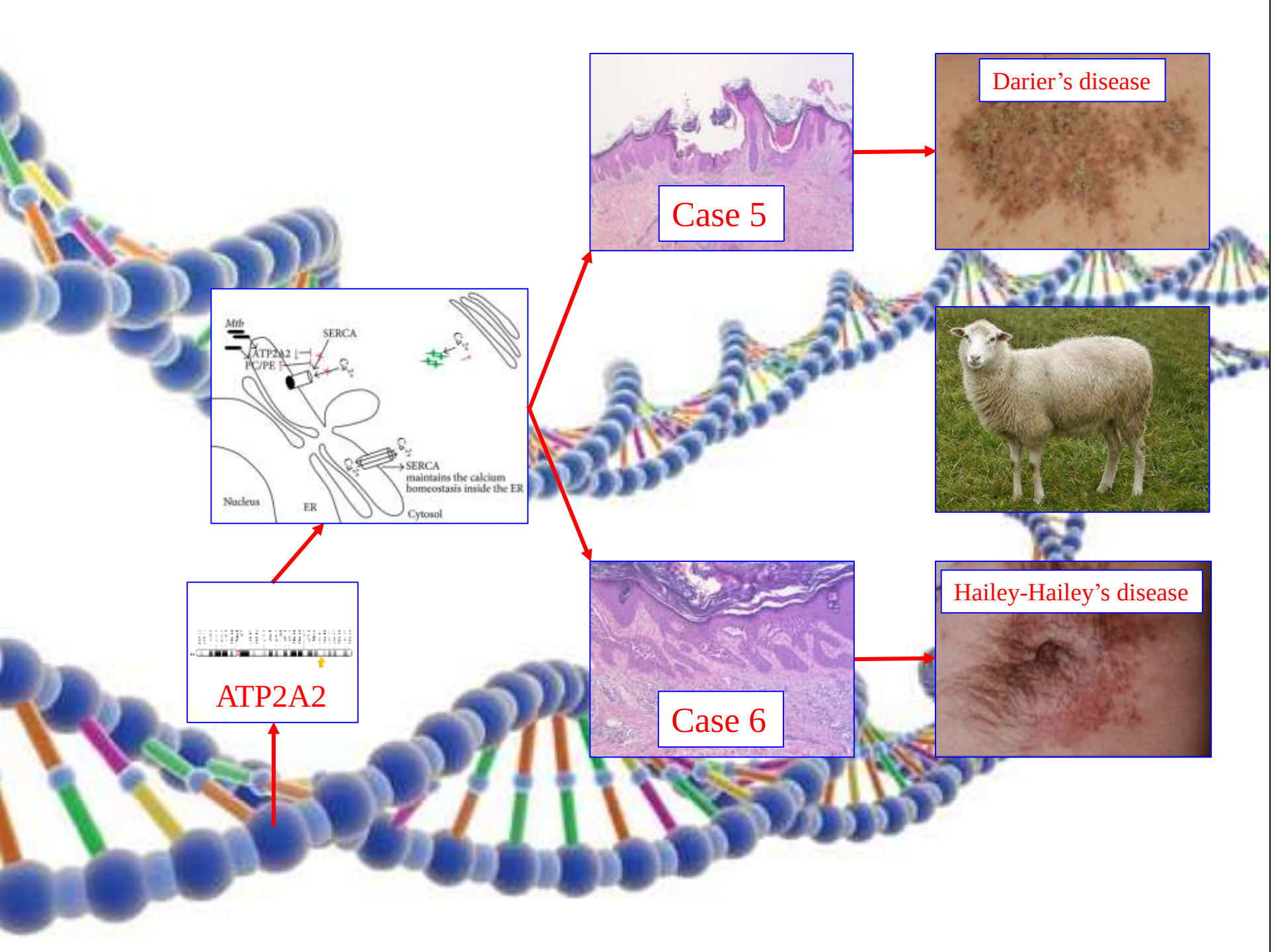
Vice versa, one and the same cause may cause a variety of diseases. Just think of staphylococci that may enter the body in different ways and may elicit an immune response influenced by many factors, including genetic ones. The interplay of those factors may result in different diseases, ranging from folliculitis to bullous impetigo and erysipelas, as shown in our case 4.



The same applies to genetic diseases. For example, Darier's disease is caused by a mutation in the ATP2A2 gene involved in epidermal calcium metabolism. Nonetheless, many patients carrying the mutation are free of disease until additional factors, such as heat or mechanical irritation, lead to manifestation of it.

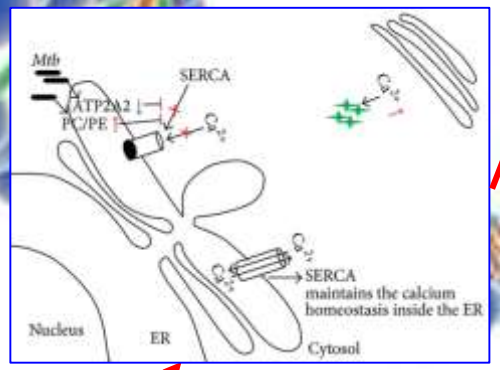


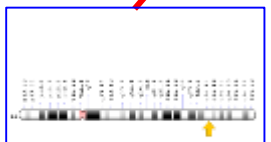
Mutations in the same gene are also responsible for Hailey-Hailey's disease that differs strikingly from Darier's disease in its clinical manifestations and its histopathologic features, with incomplete acantholysis throughout the epidermis, rather than focal suprabasal acantholysis with dyskeratoses, as shown in our cases 5 and 6. Moreover, a variety of different mutations in the gene has been described for both diseases. Of course, one could argue that a different mutation makes up a different disease but, by the same measure,



one could not accept sheep as a species because sheep also differ from one another genetically. Such differences on an individual level are implied in the concept of species, "species" being the first unifying category beyond the level of individuals. They do not require identity of their members but a close inherent relationship that elicits a series of events leading to the same net phenotypic result.

In recent years, the phenotype has often been neglected, the focus being on the genotype alone, and the view has found wide acceptance that diseases as such have no real existence



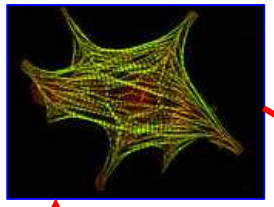


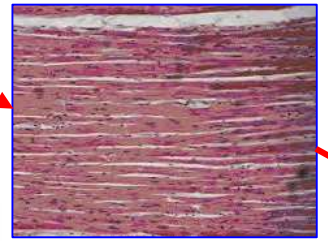
DERMATOPATHOLOGY: PRACTICAL & CONCEPTUAL

The word "disease" is a useful linguistic device, … but in the final analysis, it seems to be little more than a middleman. Our focus must be on the phenomena themselves … It is inevitable that today's notion of "disease" … will become extinct.

Jonathan Sanders, 2003

but are just words paraphrasing changes on a molecular level. In the third issue of "Dermatopathology: Practical and Conceptual," Jonathan Sanders noted that *"the word 'disease' is a useful linguistic device, … but in the final analysis, it seems to be little more than a middleman. Our focus must be on the phenomena themselves. … It is inevitable that today's notion of 'disease' … will become extinct."*



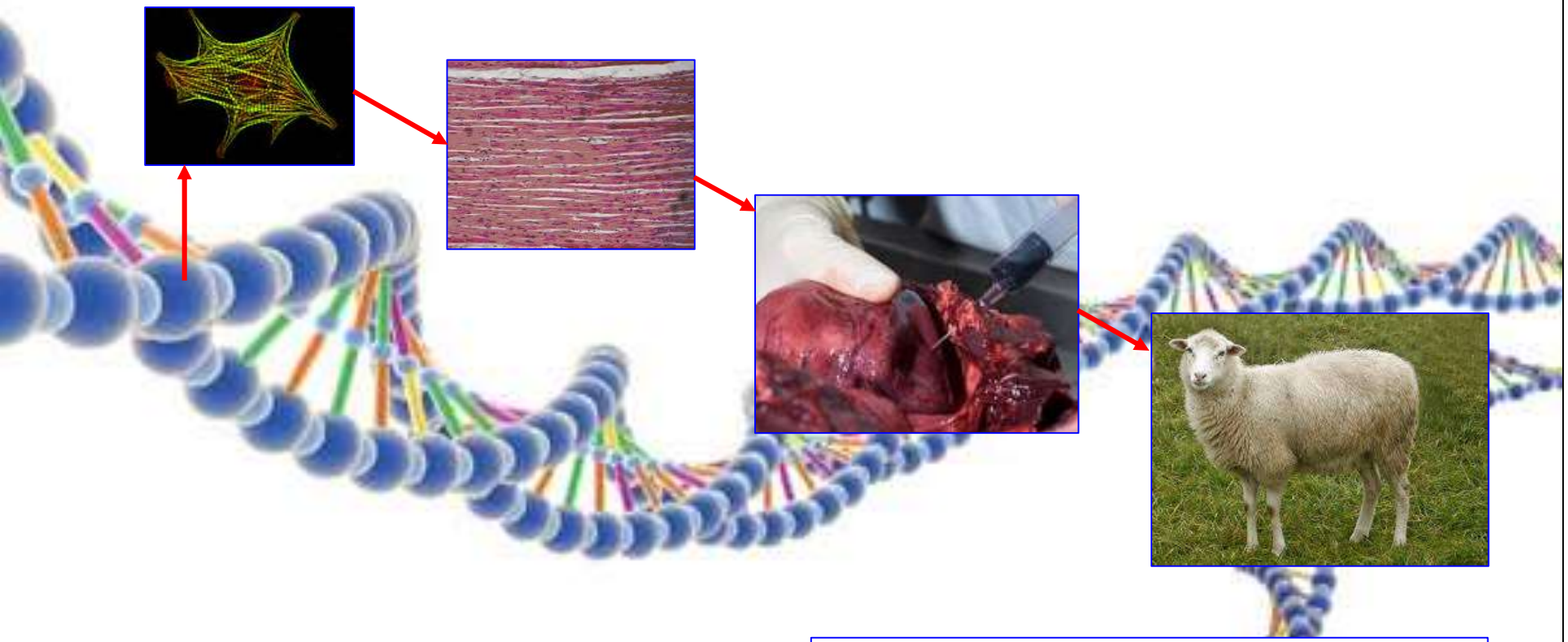


DERMATOPATHOLOGY: PRACTICAL & CONCEPTUAL

The word “disease” is a useful linguistic device, … but in the final analysis, it seems to be little more than a middleman. Our focus must be on the phenomena themselves … It is inevitable that today’s notion of “disease” … will become extinct.

Jonathan Sanders, 2003

As we have seen, similar views have been uttered in biology at large. They have been discarded because of the phenomenon of emergence. No single factor explains the net result.

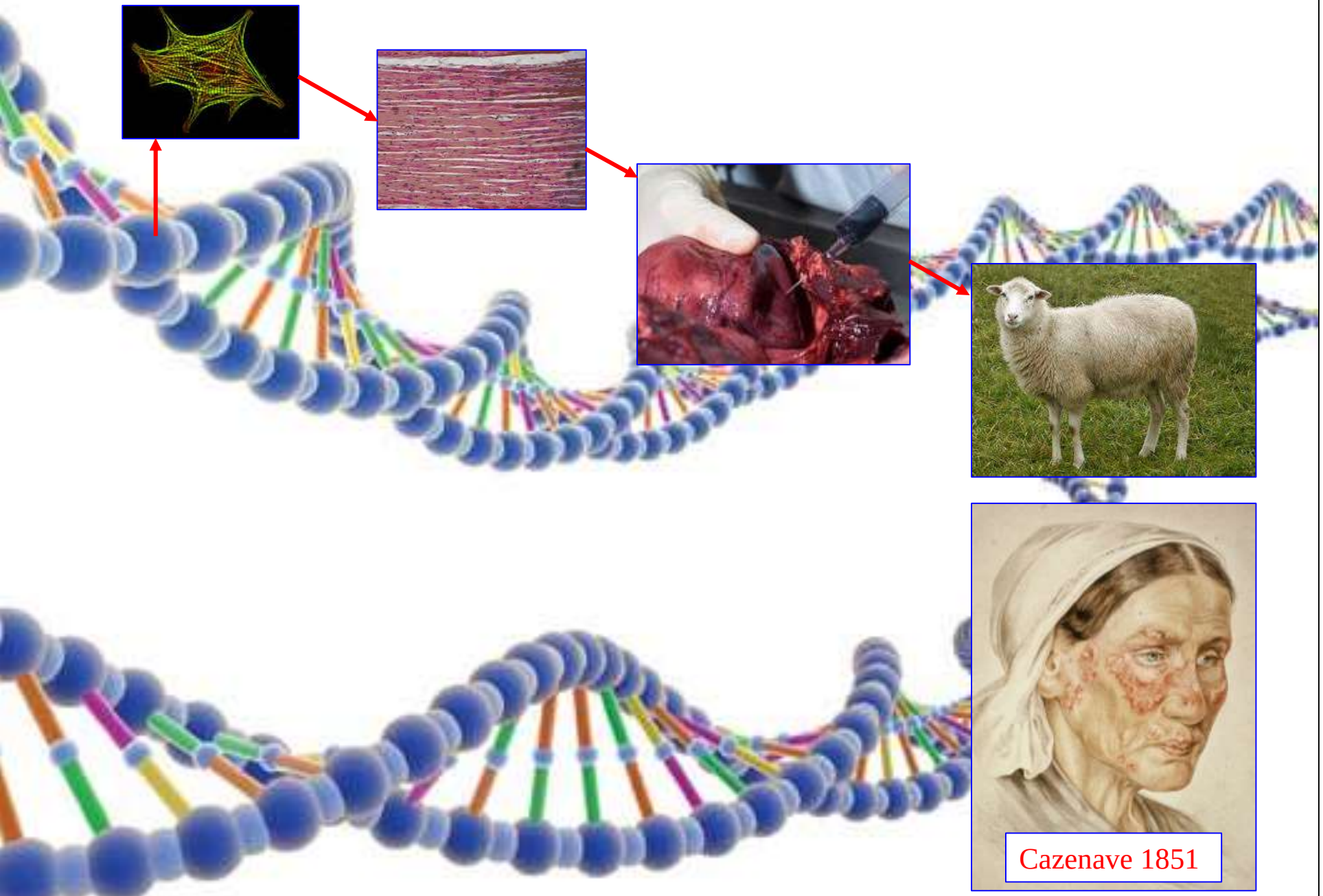


There is no connection between the molecular event and its potential significance ... since new and previously unpredictable characters emerge at higher levels of complexity in hierarchical systems. Hence, complex systems must be studied at every level.

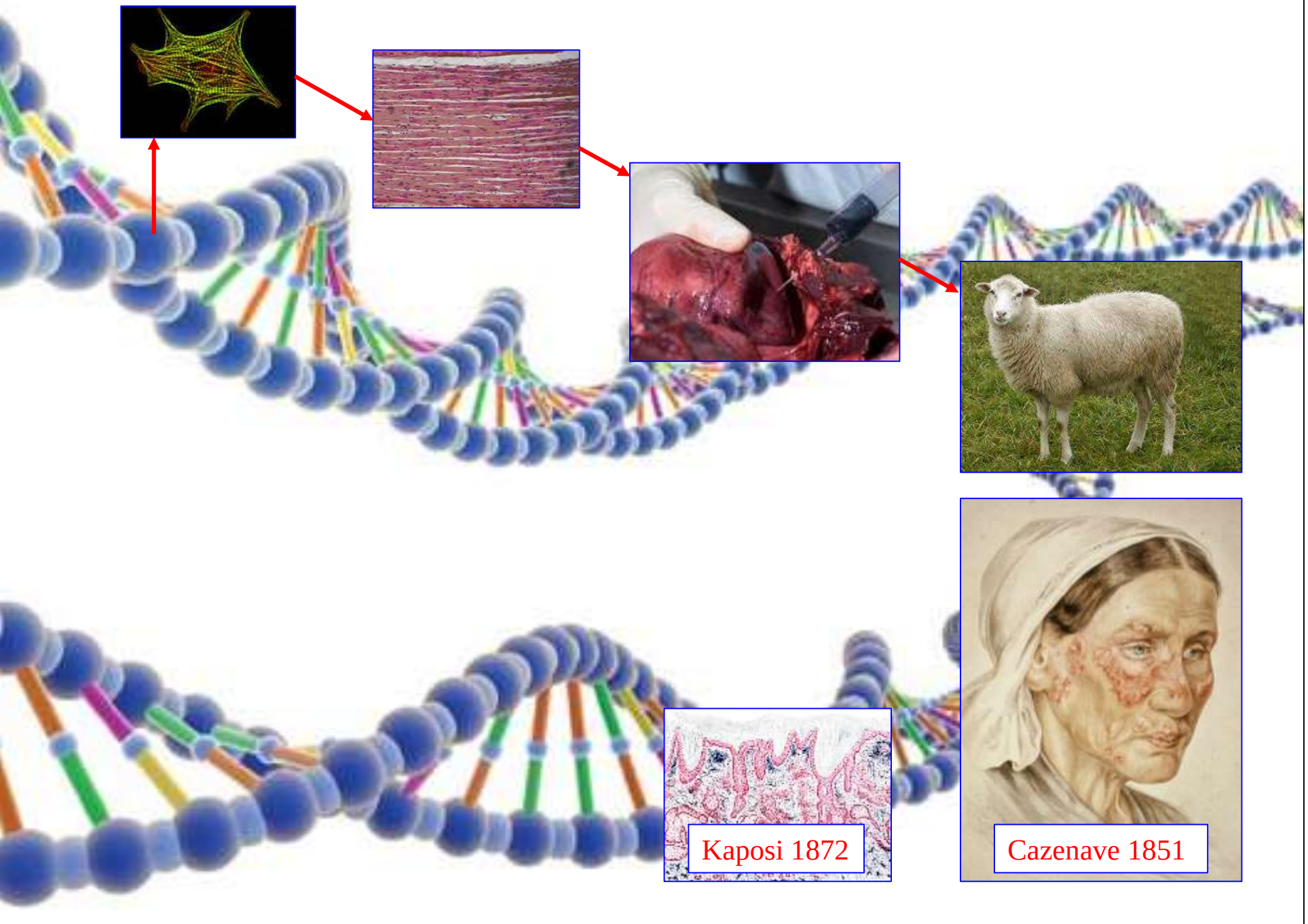
Ernst Mayr, 1982

As biologist Ernst Mayr pointed out, *"there is no connection between the molecular event and its potential significance … since new and previously unpredictable characters emerge at higher levels of complexity in hierarchical systems. Hence, complex systems must be studied at every level."*

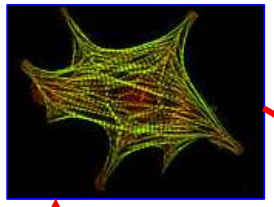
In that endeavor, the phenotype is of utmost importance.

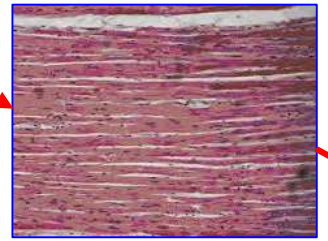


Nearly all inflammatory skin diseases have been recognized as distinct entities because of their phenotype, their distinctiveness being confirmed much later by additional findings. For example, lupus erythematosus was first described by Alphée Cazenave in 1851 on the basis of clinical findings alone.



In 1872, Kaposi added histopathologic findings and was the first to allude to extracutaneous manifestations of the disease. Yet, for many decades to come, the distinctiveness of lupus erythematosus was denied.





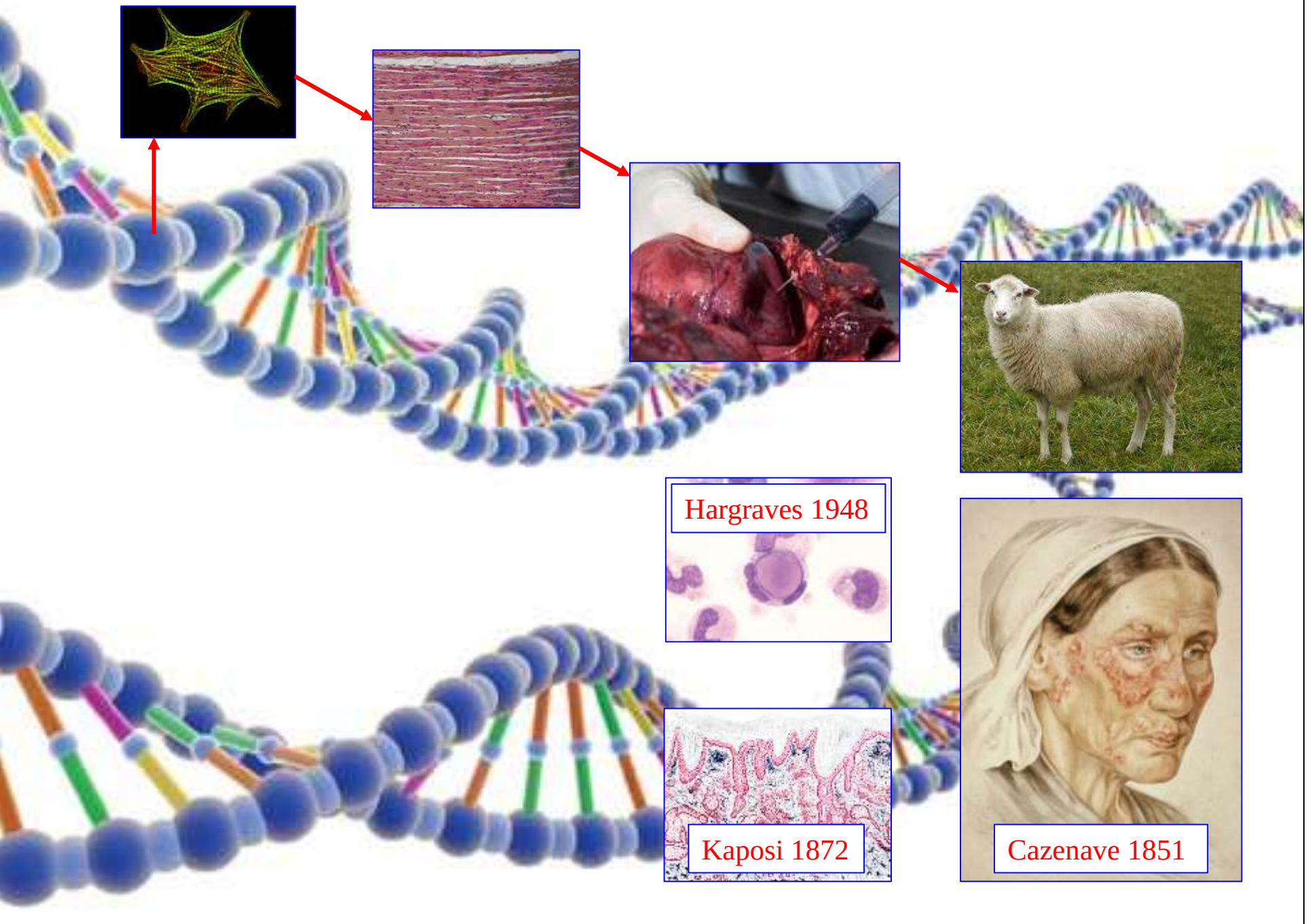
Lupus … is not a specific, not even a well specialised, disease. ... Just as insanity is sanity with modifications more or less marked, … so is lupus common inflammation of the skin with modifications, and just so is it impossible always to distinguish it from other recognised forms of skin-disease. The attempt to do so is, indeed, a mistake in clinical observation – an endeavour to make nature fit herself to moulds which are not of her making.

J. Hutchinson, 1880

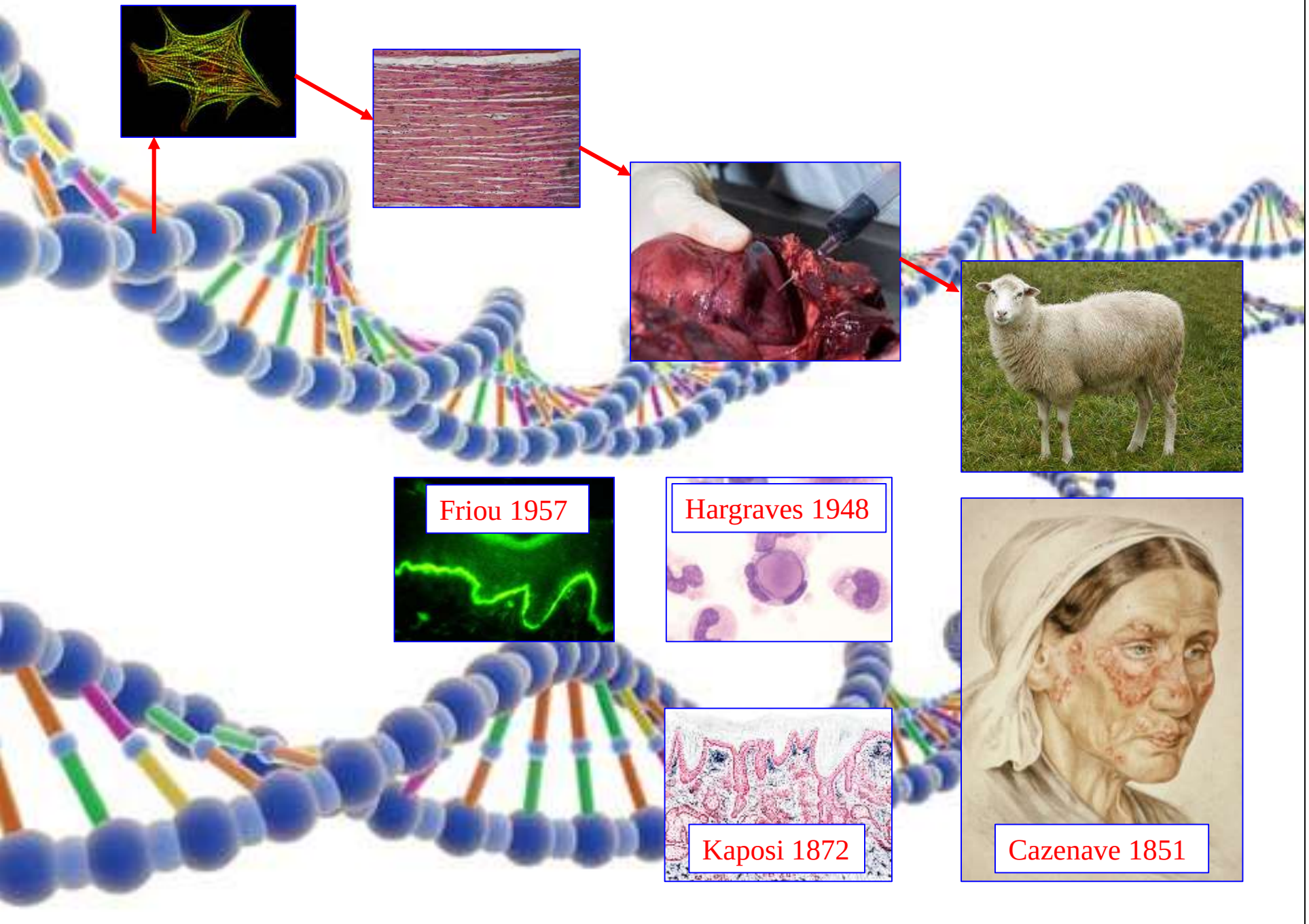
Kaposi 1872

Cazenave 1851

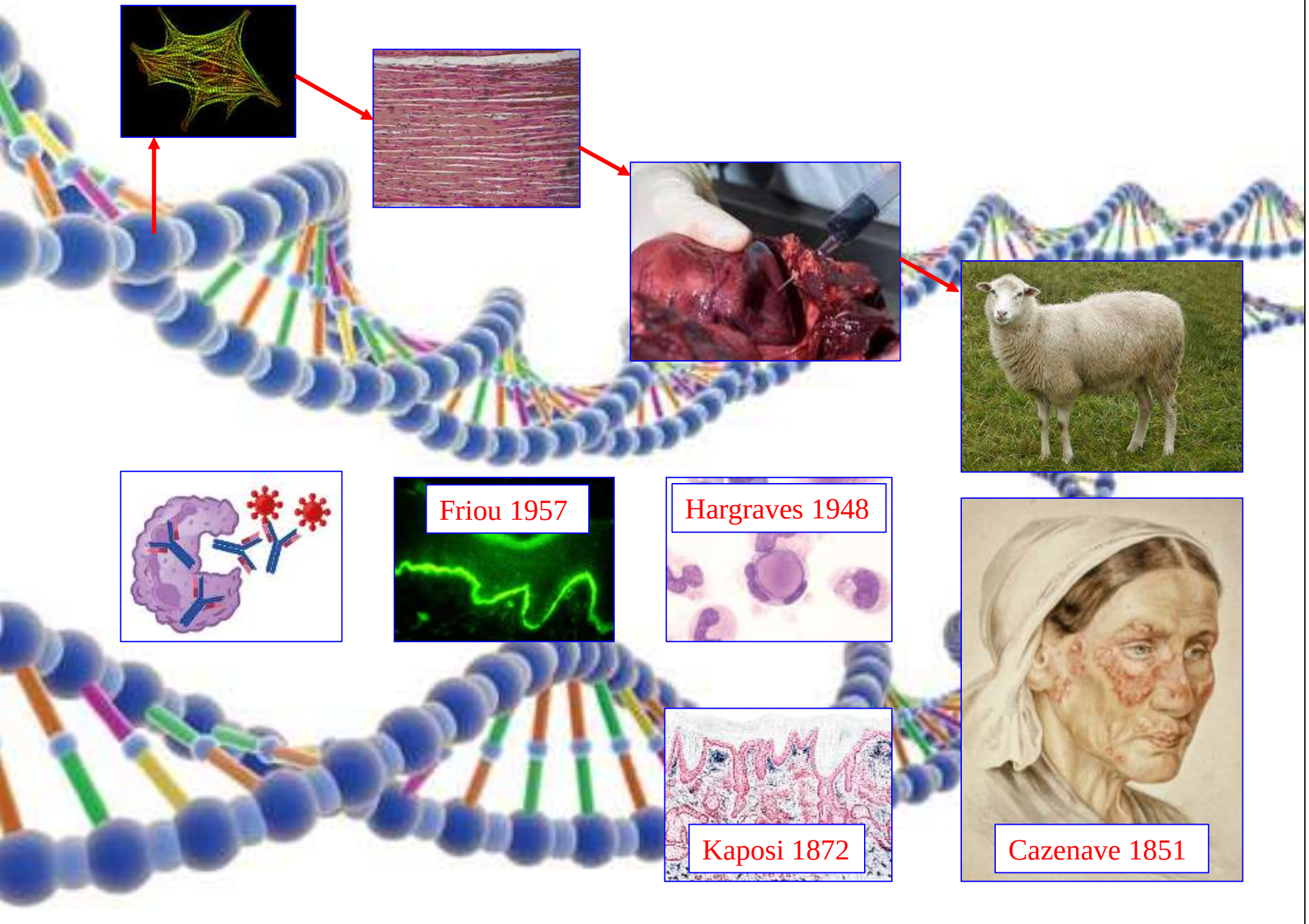
For example, Jonathan Hutchinson claimed in 1880 that *"lupus … is not a specific, not even a well specialised, disease. ... Just as insanity is sanity with modifications more or less marked, … so is lupus common inflammation of the skin with modifications, and just so is it impossible always to distinguish it from other recognised forms of skin-disease. The attempt to do so is, indeed, a mistake in clinical observation – an endeavour to make nature fit herself to moulds which are not of her making."* That nominalistic view has been overcome by additional observations,



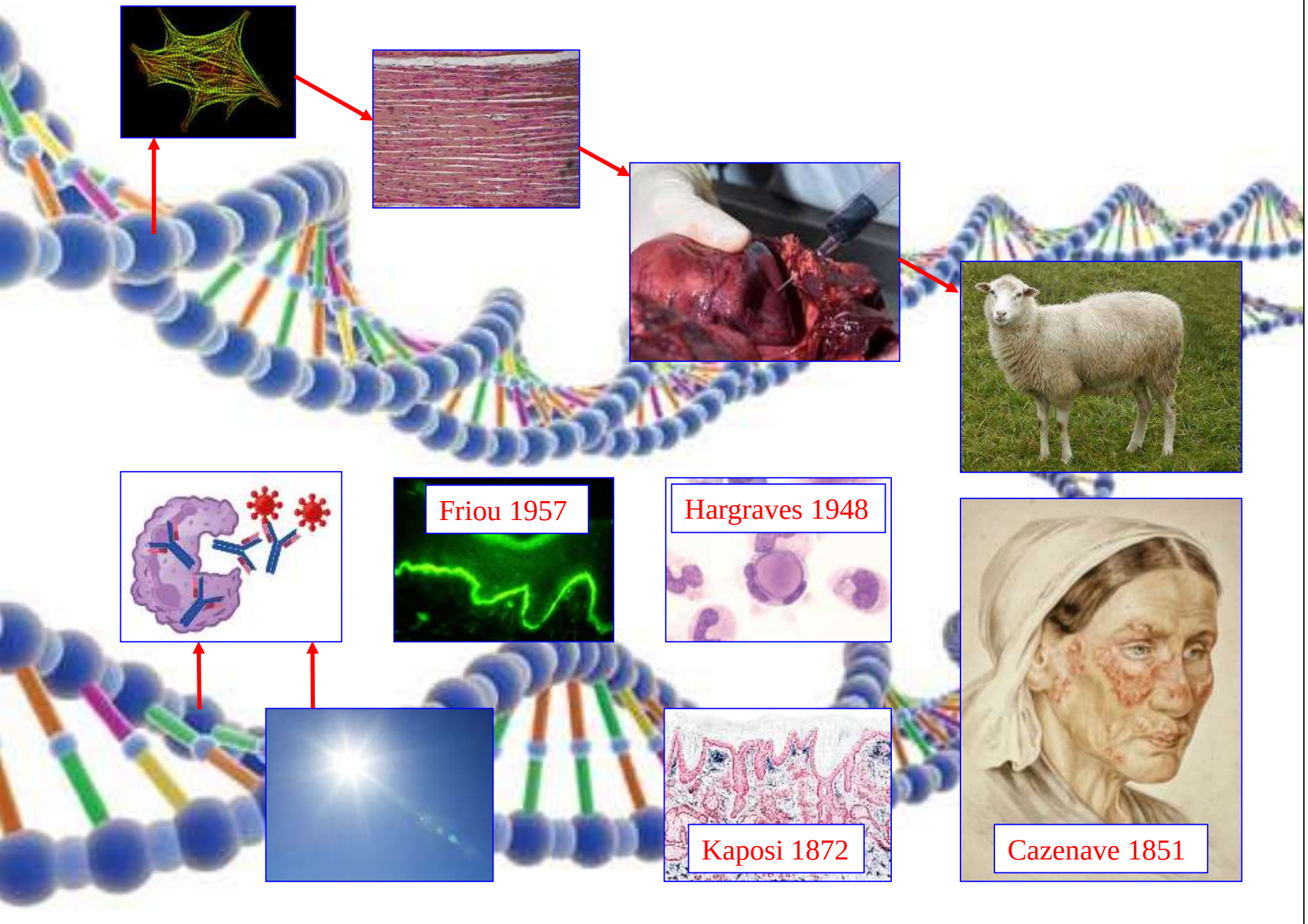
such as the description of the “LE cell” by Hargraves in 1948



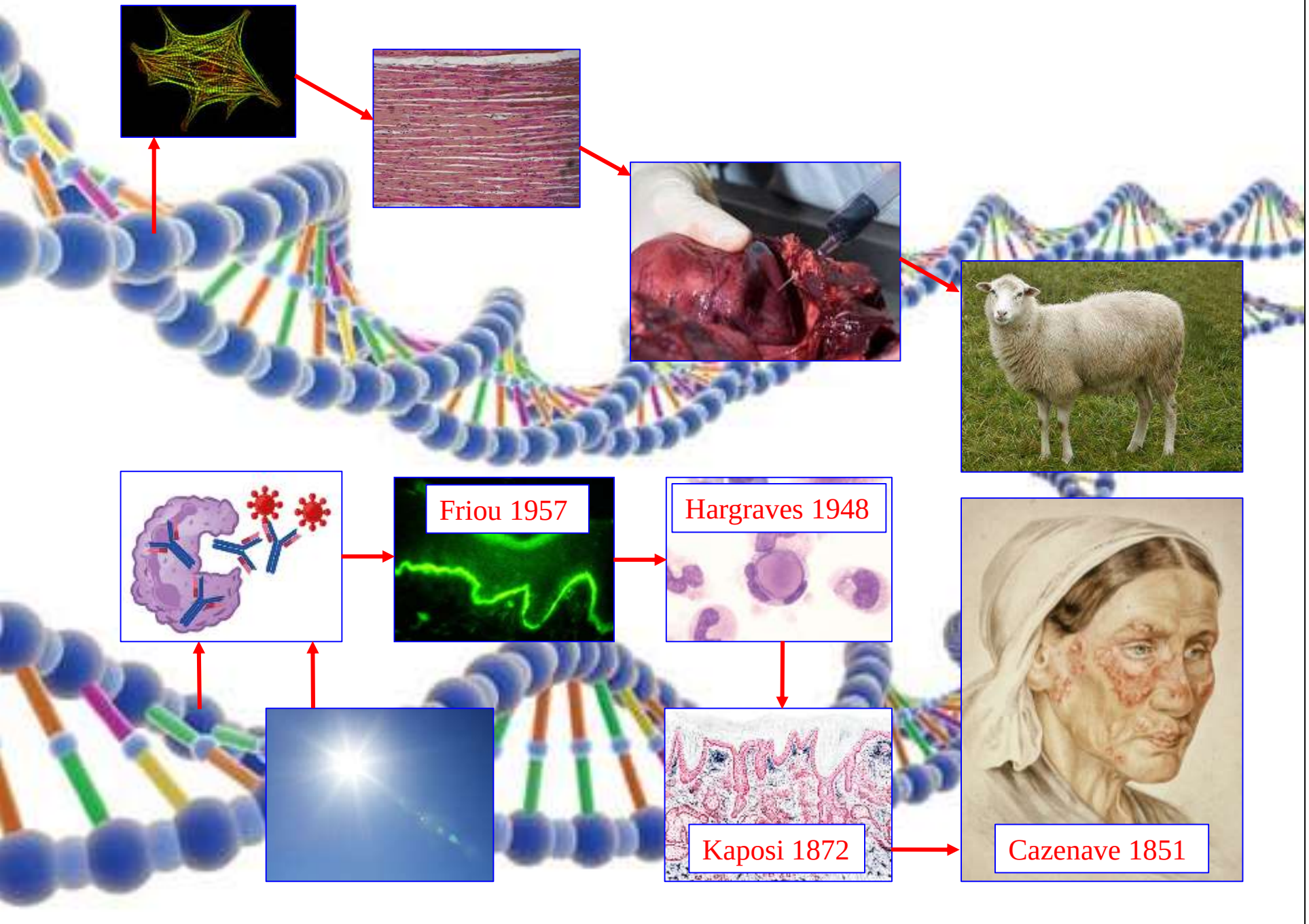
and the finding by Friou in 1957 that it was be caused by antinuclear antibodies that were eventually detected at the dermoepidermal junction.



Those antibodies were characterized further,



a genetic predisposition was recognized, and other pathogenetic factors were described, such as activation of the disease through UV irradiation.



Together, those findings provide a coherent picture of the disease as a unique pathologic process, despite all variants and equivocal cases.

Of course, when discussing the specificity of diagnosis, it must be acknowledged that biologic species and diseases cannot be equated with one another. The principles of recognition and classification of entities, however, are the same,

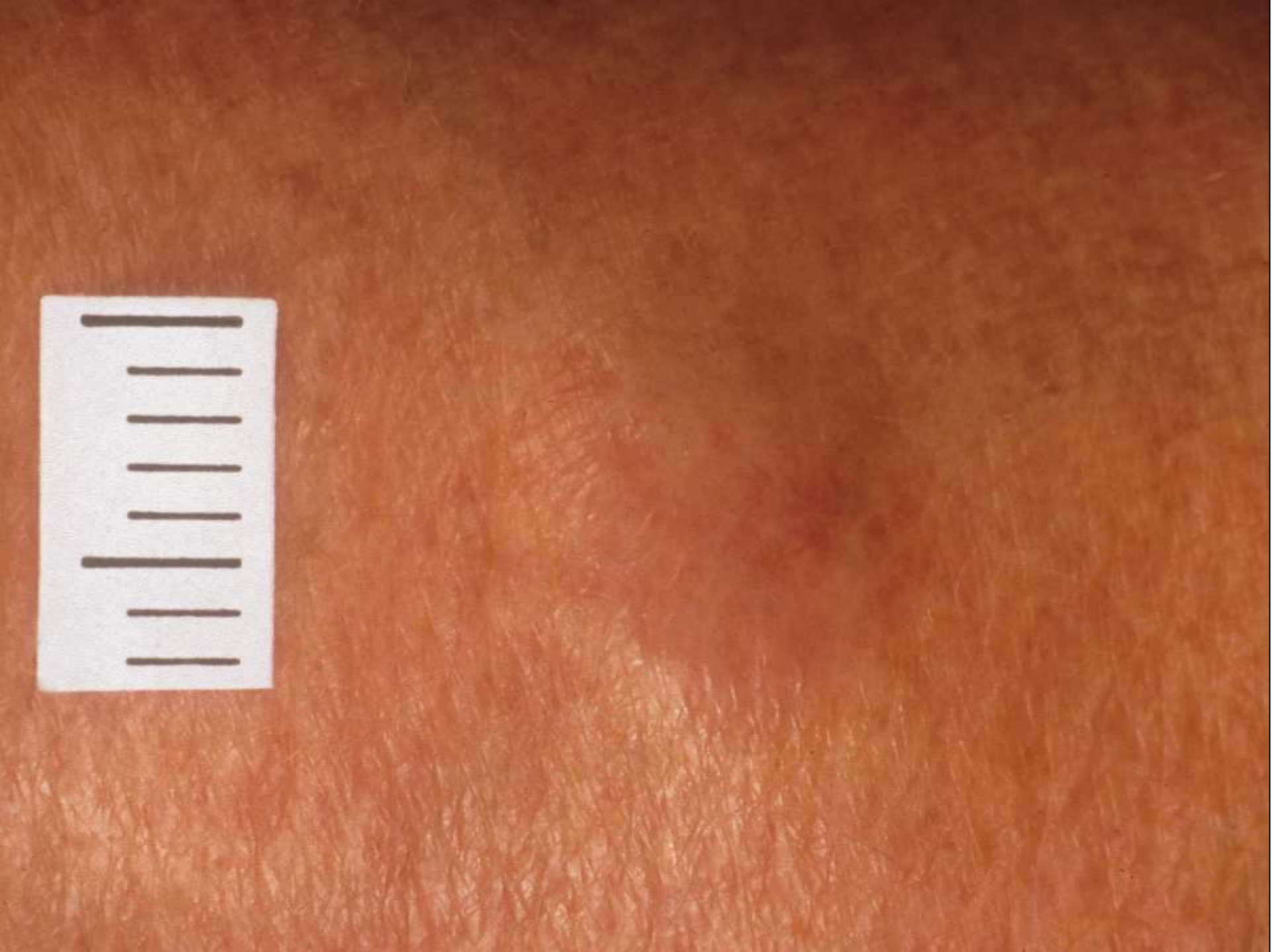
reproductive isolation

including the criterion of reproductive isolation. The first diseases to be recognized as distinct entities were contagious ones that were passed on, in stereotypic fashion, from one patient to the next so that the criterion of reproductive isolation was fulfilled.

In regard to other diseases, that criterion is either not applicable at all, or in only limited fashion,

reproductive isolation

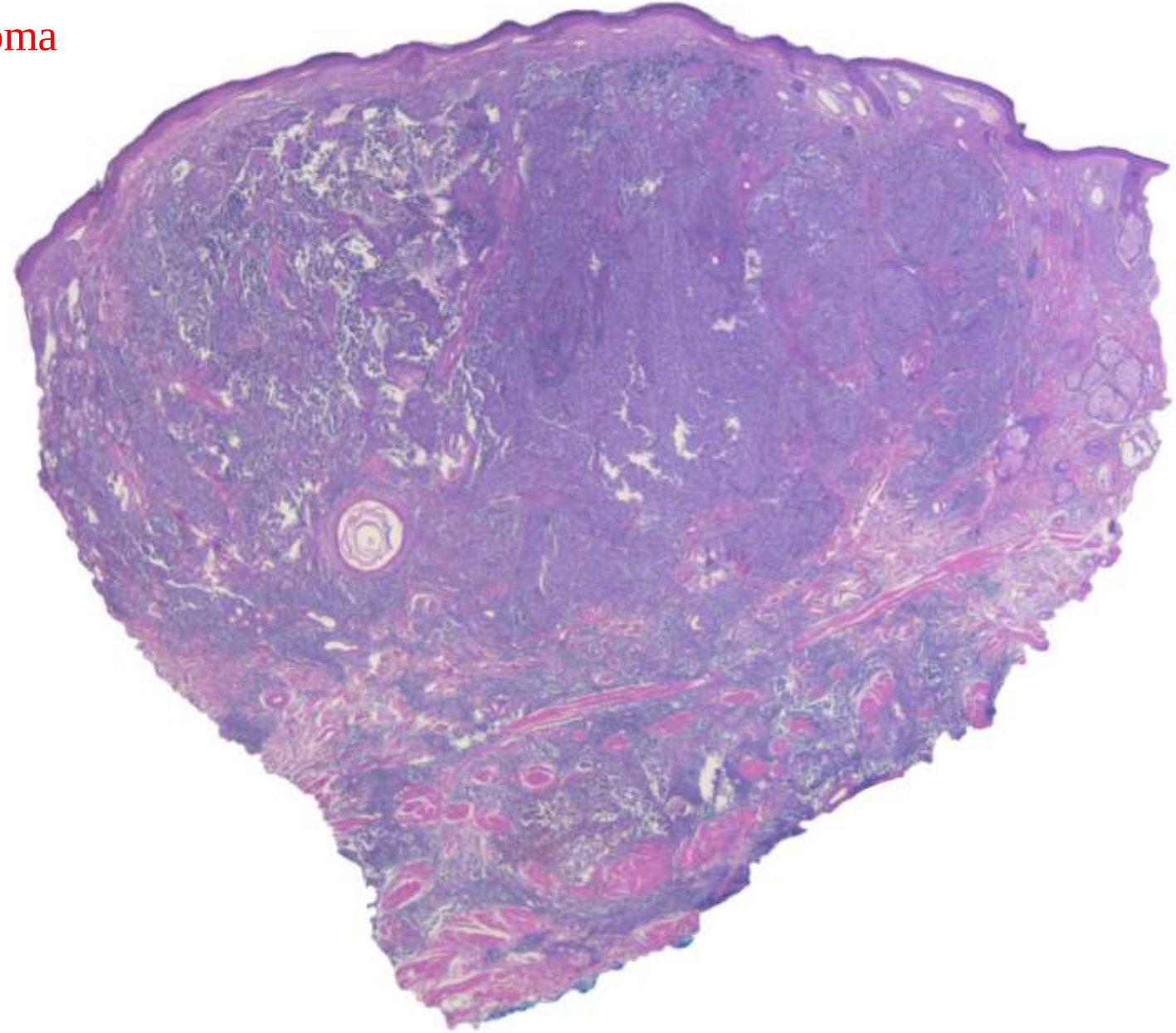
as for neoplasms that are caused by a clonal expansion of cells so that, at least in this sense, reproductive isolation is at play. Therefore, recognition of biologic entities should be easier in the realm of neoplasia than in inflammatory diseases – but this is not the case.



The chief reason is that neoplasms are usually solitary lesions and, therefore, less distinctive clinically because criteria such as distribution and arrangement cannot be applied. Because of their indistinct clinical presentation,

Merkel cell carcinoma

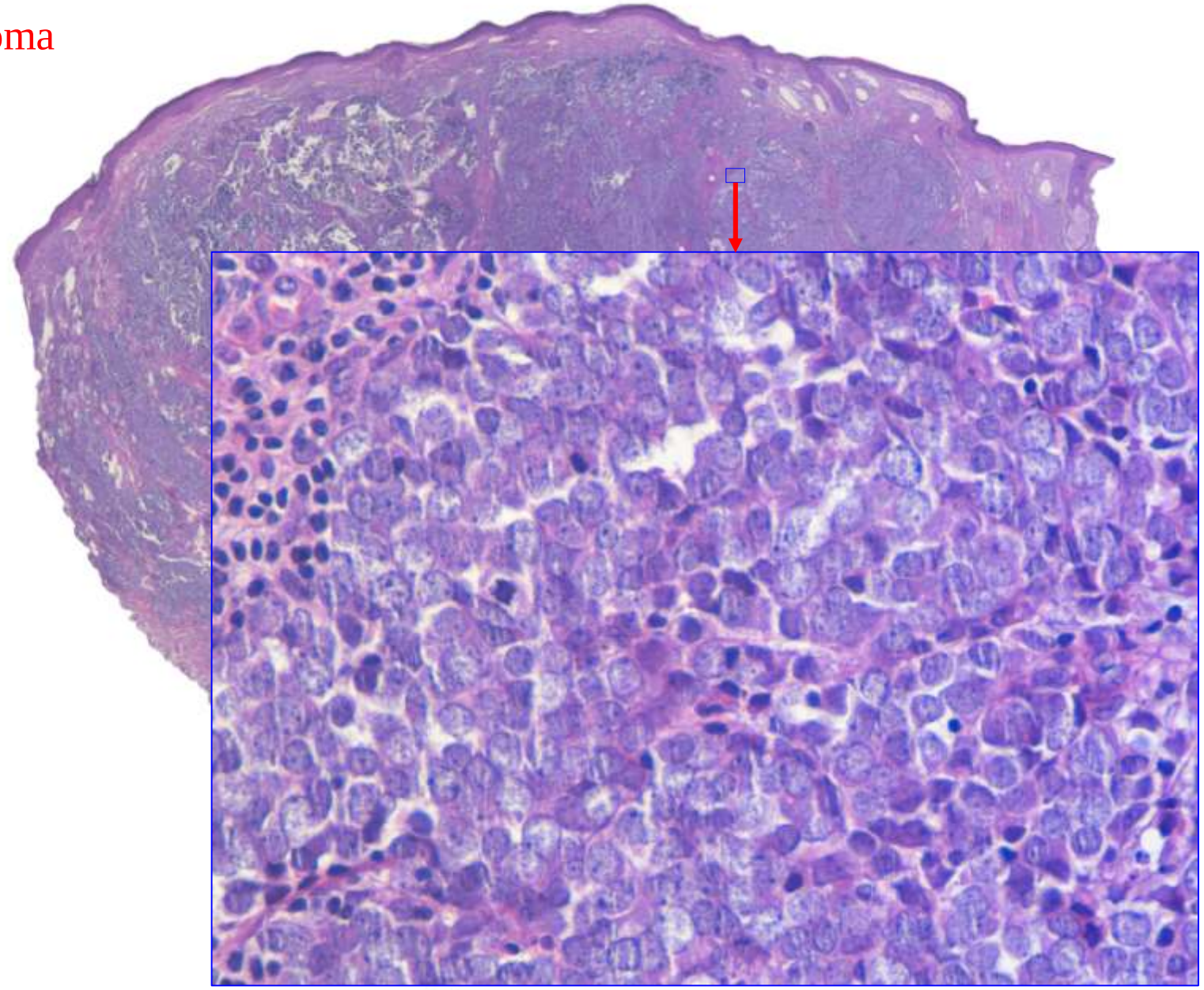
Case 7



many common neoplasms have been described relatively late. For example, Merkel cell carcinoma was not described before 1972,

Merkel cell carcinoma

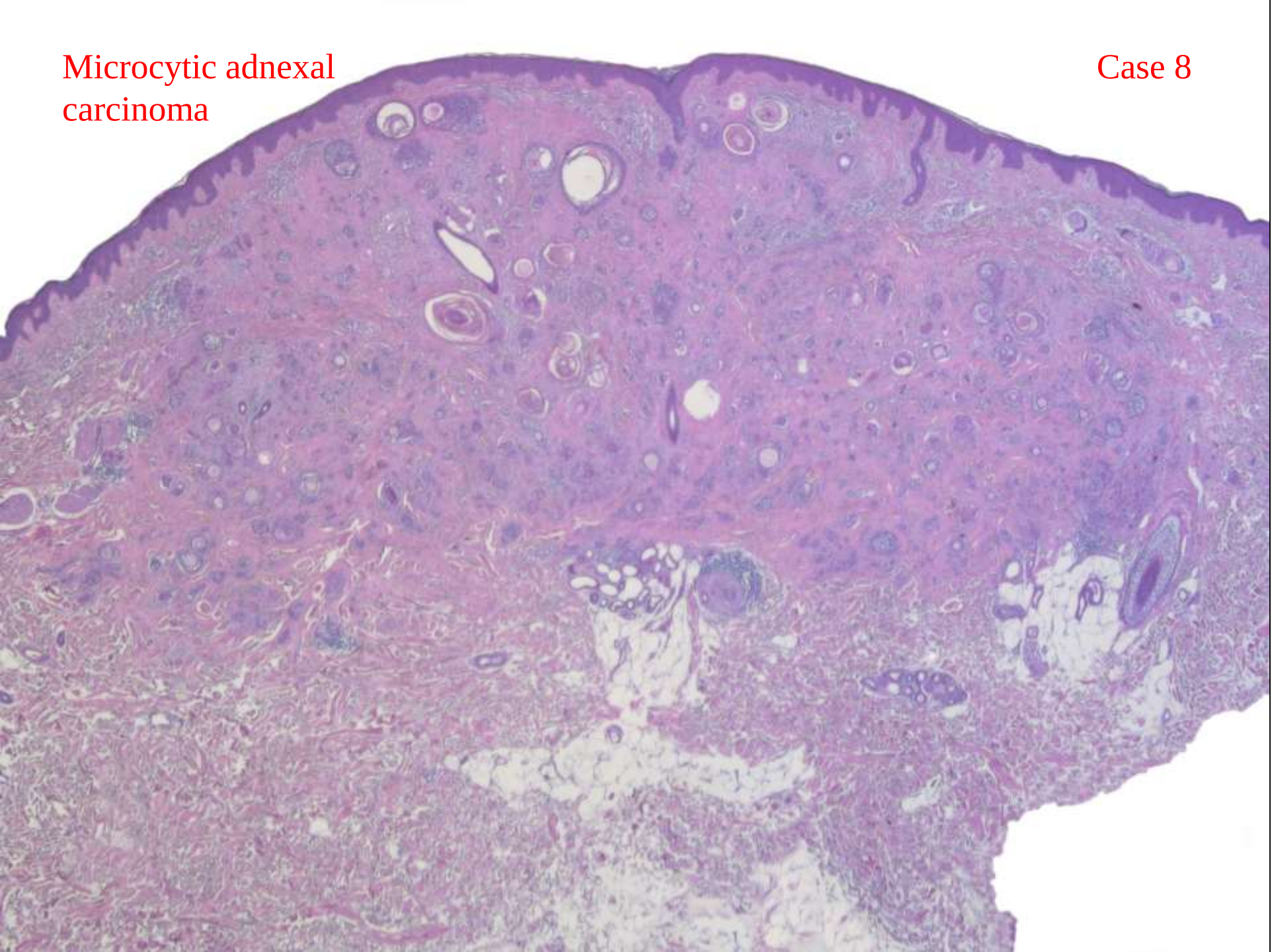
Case 7



despite its highly characteristic cytologic features – monomorphous round to oval cells with granulated nucleoplasm and many mitotic figures, as shown in our case 7.

Microcytic adnexal carcinoma

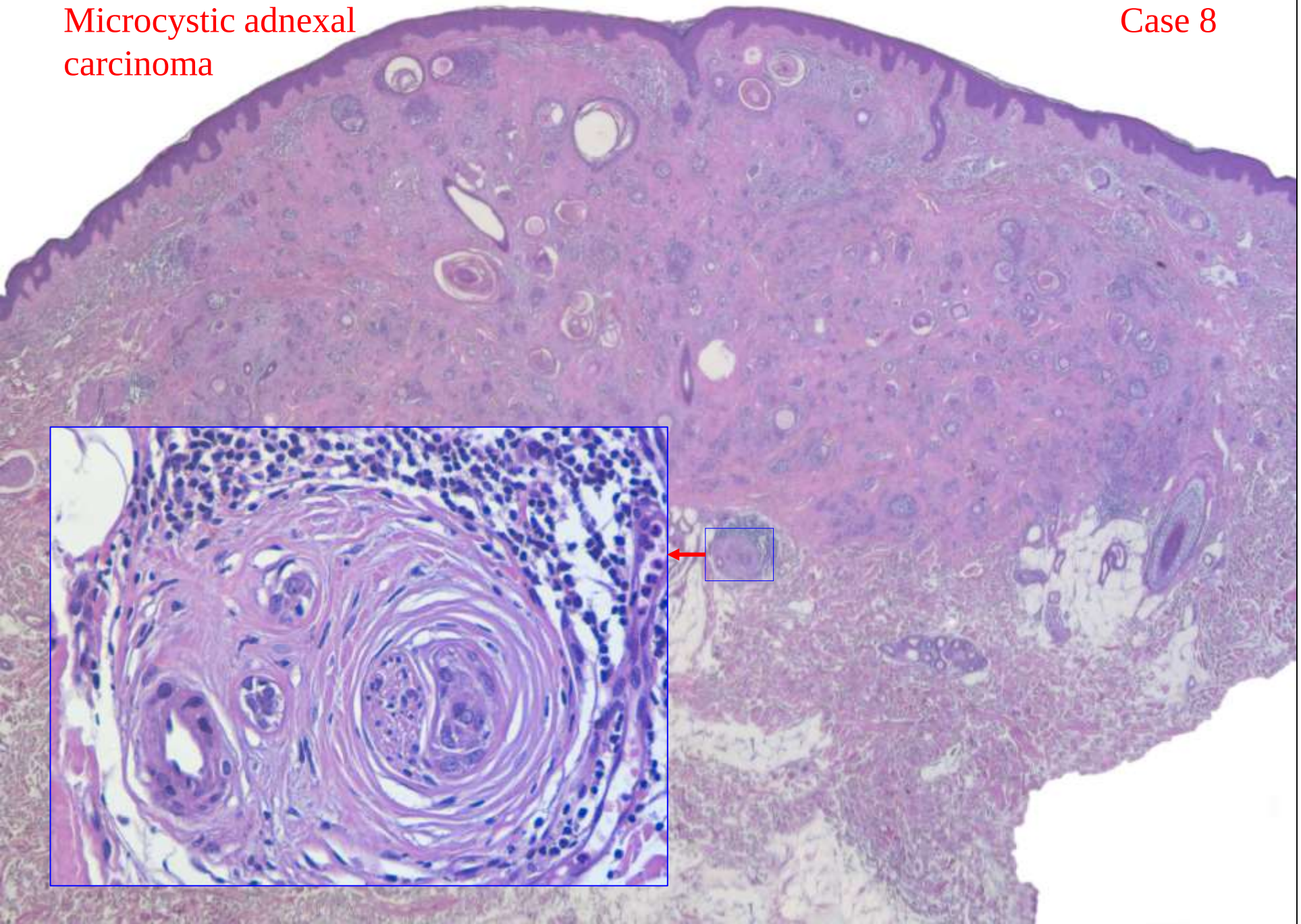
Case 8



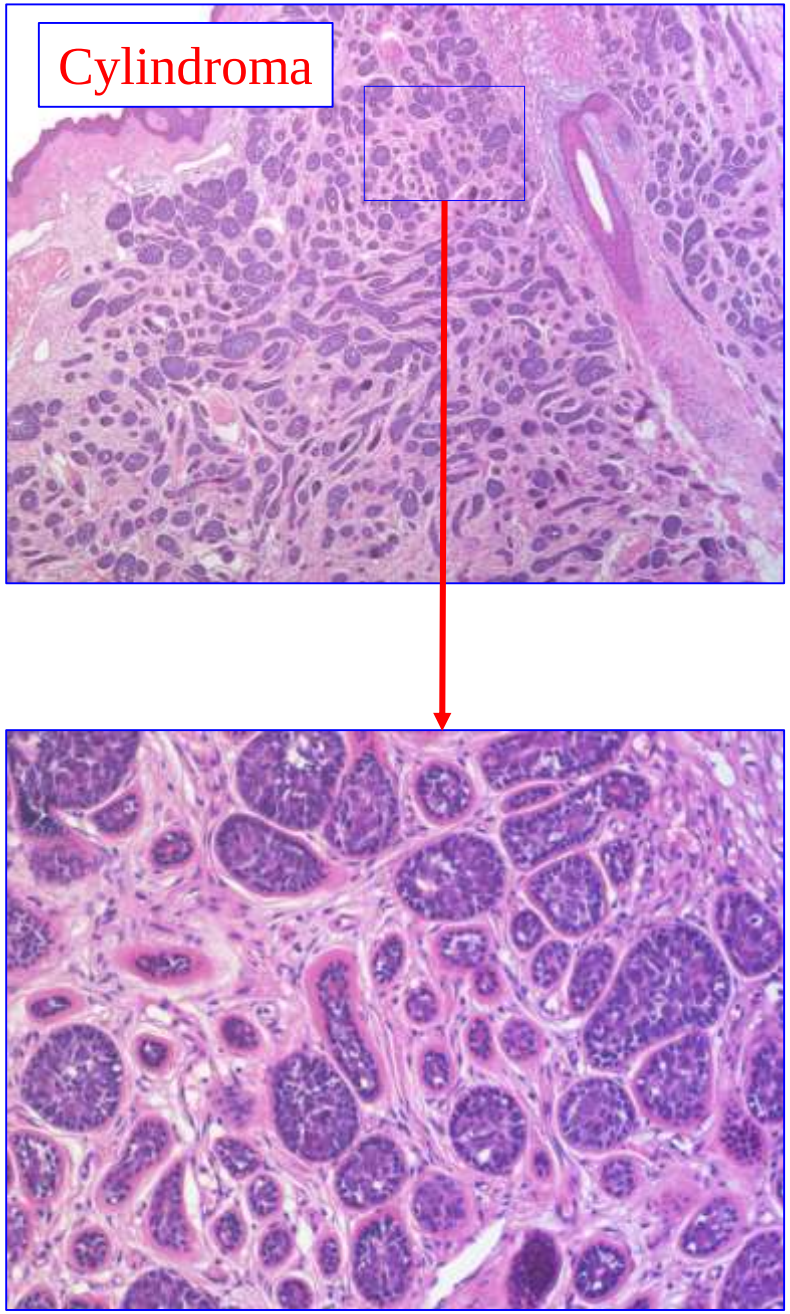
Microcystic adnexal carcinoma, shown in our case 8, was even described ten years later, although its architecture – numerous cysts in the superficial and tubular structures in the deep dermis,

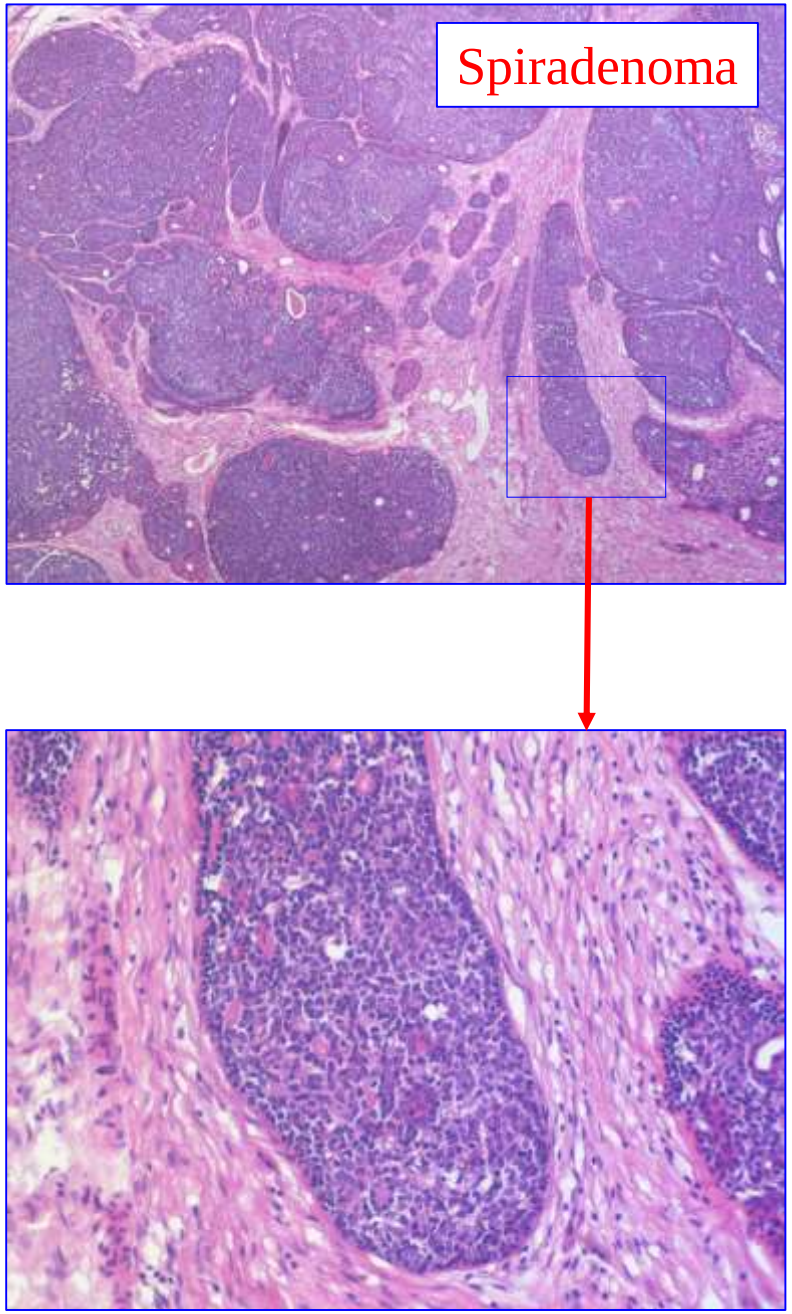
Microcystic adnexal carcinoma

Case 8

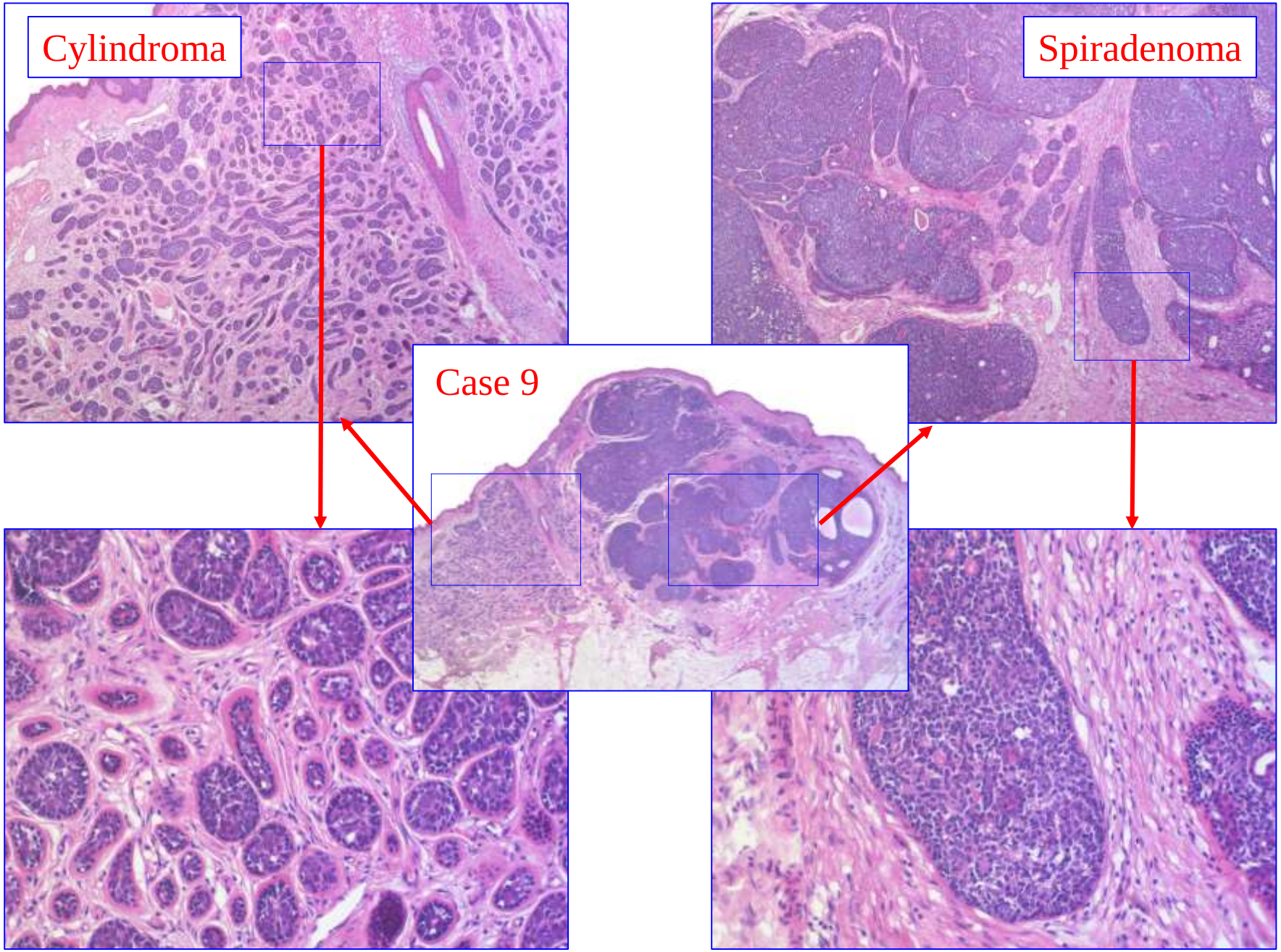


together with neurotropism – is also highly characteristic. Undoubtedly, there are many other neoplasms still waiting to be distinguished as separate entities.

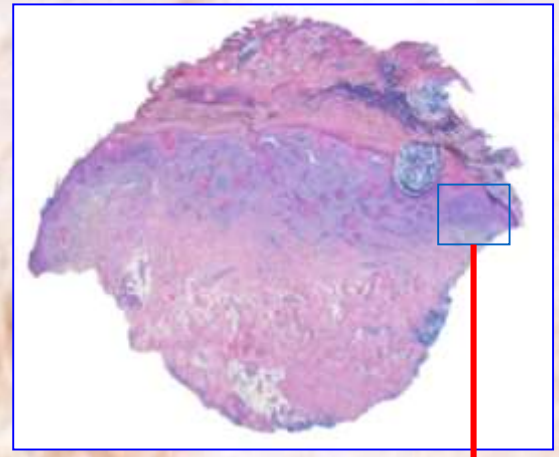


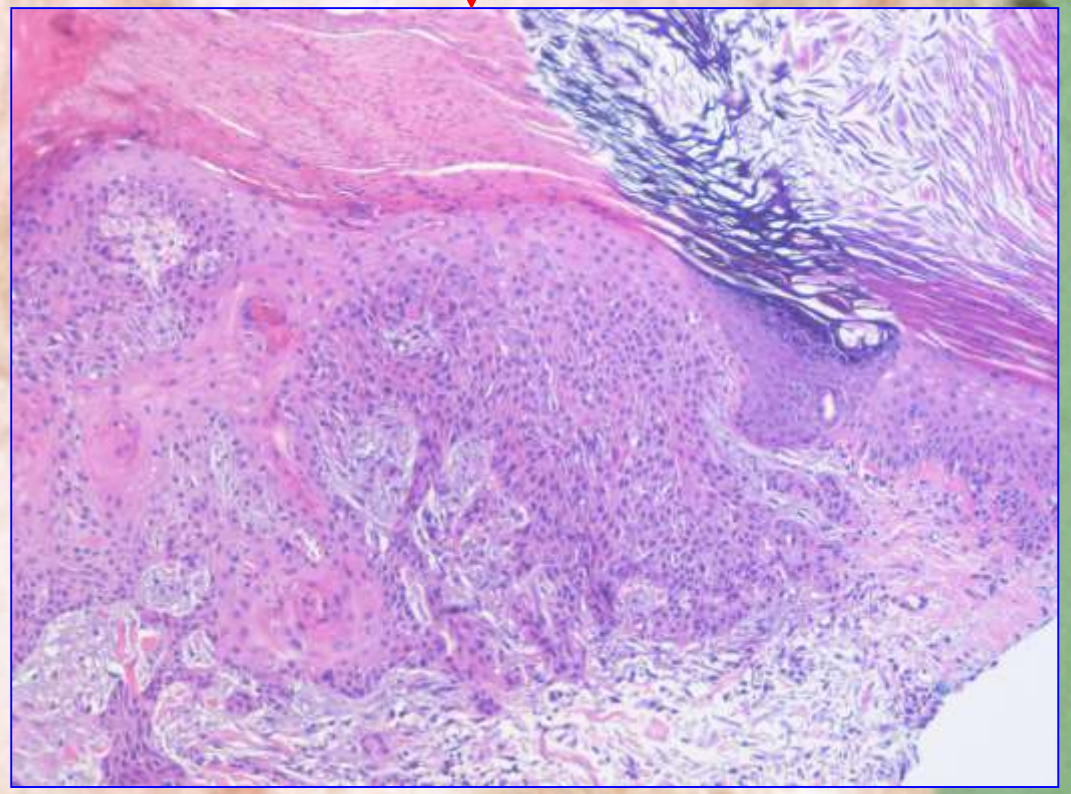


Vice versa, many neoplasms have been described as distinct entities that are now considered to be morphologic variants of the same process, usually because features thought to be specific for either of them

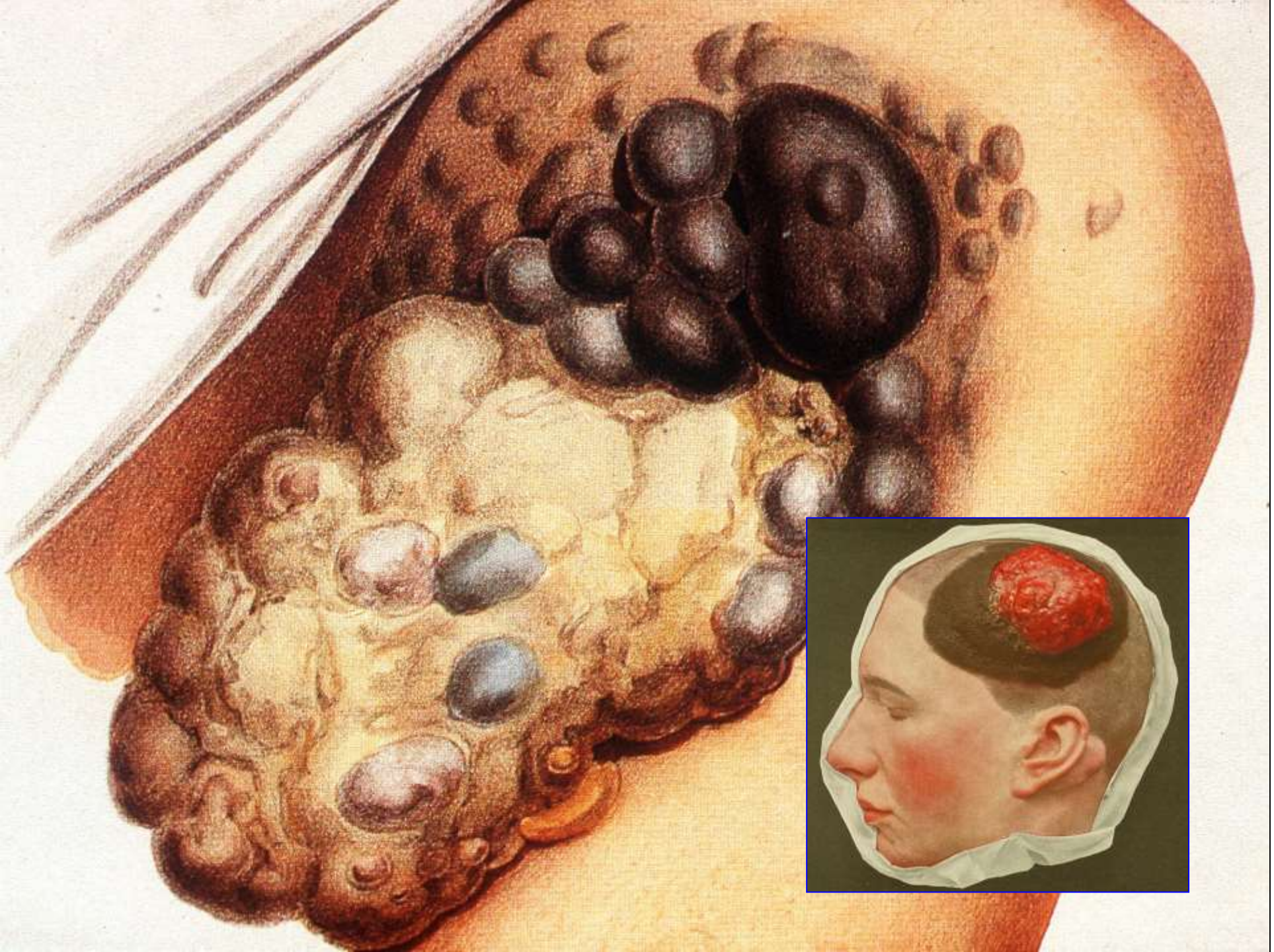


were eventually found repeatedly within the same lesion, cylindroma and spiradenoma being one example, as shown in case 9.





In addition to morphologic variants, different stages of the same process have been described as separate entities, a lapse caused not only by the paucity of diagnostic clinical features but also, and especially, by ingrained prejudice, namely, the antiquated view that cancer is nearly always a deadly disease.



In the 19th century, that view was established so firmly that the diagnosis was challenged if a patient survived. This was, in fact, a rare event, because the diagnosis was made only in stages far advanced.

The pigmented cancer ... begins ... with the development of roundish nodules of the size of a bruised grain, pea, or bean. ... They remain disseminated for a while, then several of them become confluent and form an irregular, bumpy, larger nodule. Moritz Kaposi, 1872

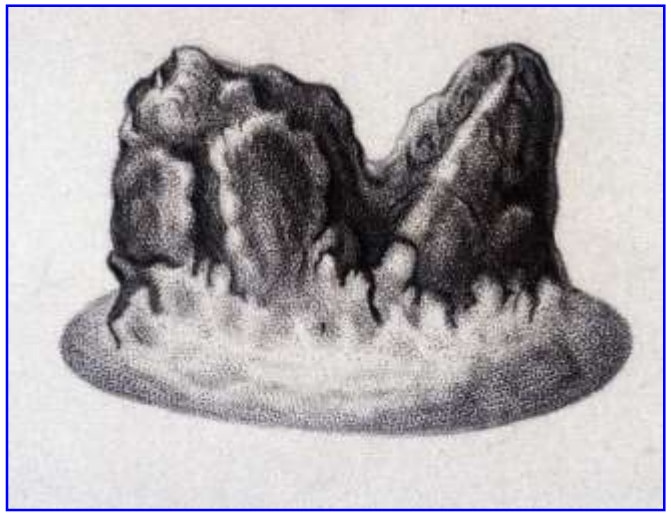
For example, melanoma was said by Kaposi to begin with *"with the development of roundish nodules of the size of a bruised grain, pea, or bean. ... They remain disseminated for a while, then several of them become confluent and form an irregular, bumpy, larger nodule."*

The large flat component of melanomas that often expands over decades was generally misinterpreted as a pre-existing nevus. Thus, late diagnosis and the assumption of a terrible prognosis of melanoma reinforced themselves mutually.

homologous neoplasms

heterologous neoplasms

benign

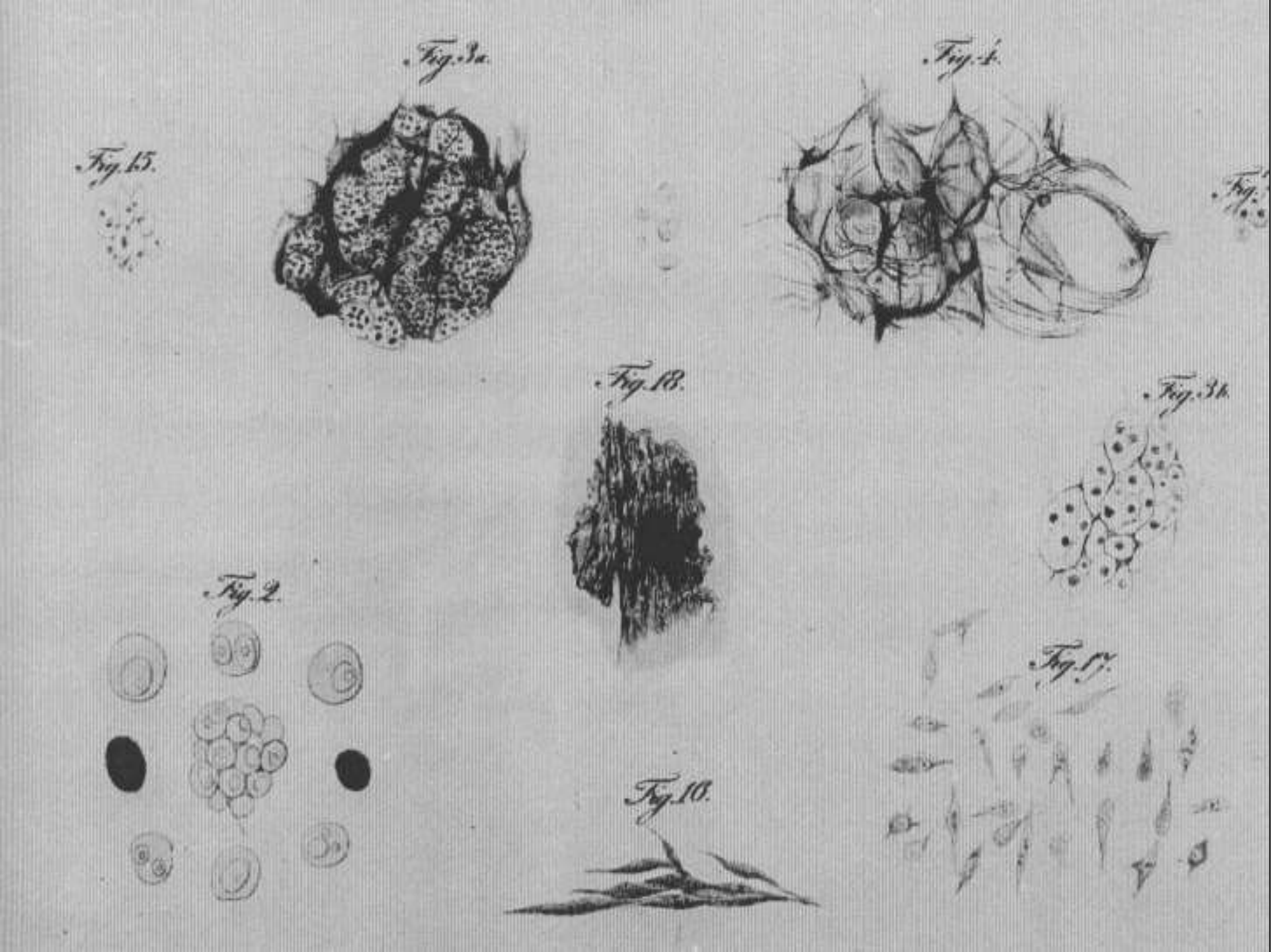


malignant

composed of normal elements of tissue

not composed of normal elements of tissue

Originally, benign and malignant neoplasms had been distinguished sharply from one another. The former, so-called “homologous” neoplasms were thought to be composed of normal elements of tissue, whereas malignant, so-called “heterologous” neoplasms were thought to be composed of elements not normally found in the human body.



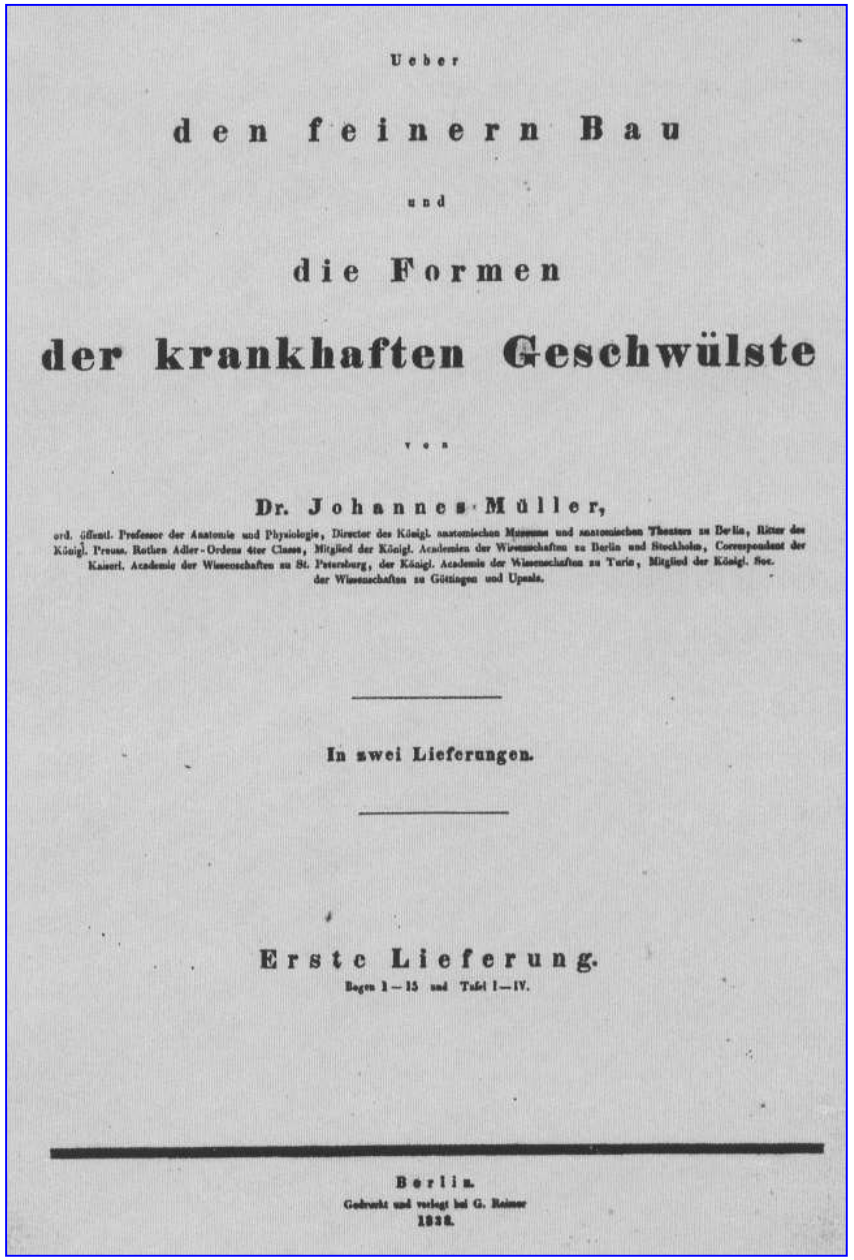
When, in the 1830s, neoplasms began to be studied microscopically, they were all found to be composed of cells.

Johannes Müller
1801-1858

A distinction of pathologic tissues into homologous and hetero-logous ones cannot be made …

In regard to its most delicate elements and genesis, the structure of the most benign neoplasms does not differ from cancer.

Johannes Müller, 1838



Ueber

den feinern Bau

und

die Formen

der krankhaften Geschwülste

von

Dr. Johannes Müller,

ord. öffentl. Professor der Anatomie und Physiologie, Director des Königl. anatomischen Museums und anatomischen Theaters zu Berlin, Ritter des Königl. Preuss. Rothen Adler-Ordens 4ter Classe, Mitglied der Königl. Academien der Wissenschaften zu Berlin und Stockholm, Correspondent der Kaiserl. Academie der Wissenschaften zu St. Petersburg, der Königl. Academie der Wissenschaften zu Turin, Mitglied der Königl. Soc. der Wissenschaften zu Göttingen und Upsala.

In zwei Lieferungen.

Erste Lieferung.

Bogen 1—15 und Tafel I—IV.

Berlin.

Gedruckt und verlegt bei G. Reimer

1838.

In the very first monograph about the histopathology of neoplasms in 1839, Johannes Müller of Berlin concluded that *"a distinction of pathologic tissues into homologous and heterologous ones cannot be made … In regard to its most delicate elements and genesis, the structure of the most benign neoplasms does not differ from cancer."*

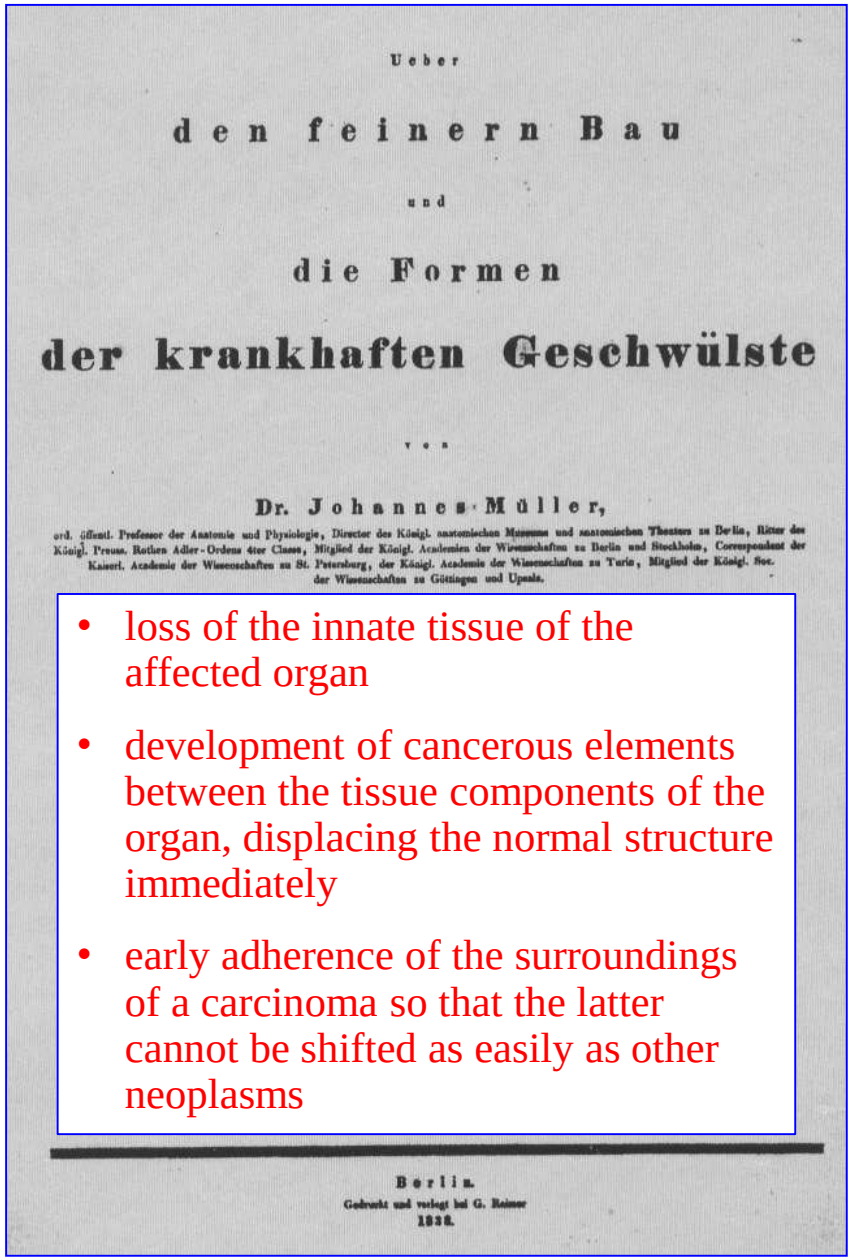
Nonetheless, Müller alluded to certain peculiarities of so-called *"cancerous degenerations,"*

Johannes Müller
1801-1858

A distinction of pathologic tissues into homologous and hetero-logous ones cannot be made …

In regard to its most delicate elements and genesis, the structure of the most benign neoplasms does not differ from cancer.

Johannes Müller, 1838



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- loss of the innate tissue of the affected organ
- development of cancerous elements between the tissue components of the organ, displacing the normal structure immediately
- early adherence of the surroundings of a carcinoma so that the latter cannot be shifted as easily as other neoplasms

Berlin.

Gedruckt und verlegt bei G. Reimer

1838.

namely, *“loss of the innate tissue of the affected organ,”* the *“development of cancerous elements between the tissue components of the organ, displacing the normal structure immediately,”* and the *“early adherence of the surroundings of a carcinoma so that the latter cannot be shifted as easily as other neoplasms.”*


Robert Remak
1815-1865

Cancer, from the outset, tends to develop in a particular way, just as eggs of animals tend to form particular structures, and one cannot believe that a cancerous neoplasm, at its beginning, could develop into anything else. … Every neoplasm already possesses its fundamental properties at its outset, which do not change over time, so that, as a rule, benign neoplasms remain benign and cancerous neoplasms are cancerous from the beginning.

Robert Remak, 1841

Medicinische Zeitung.

Zehnter Jahrgang.

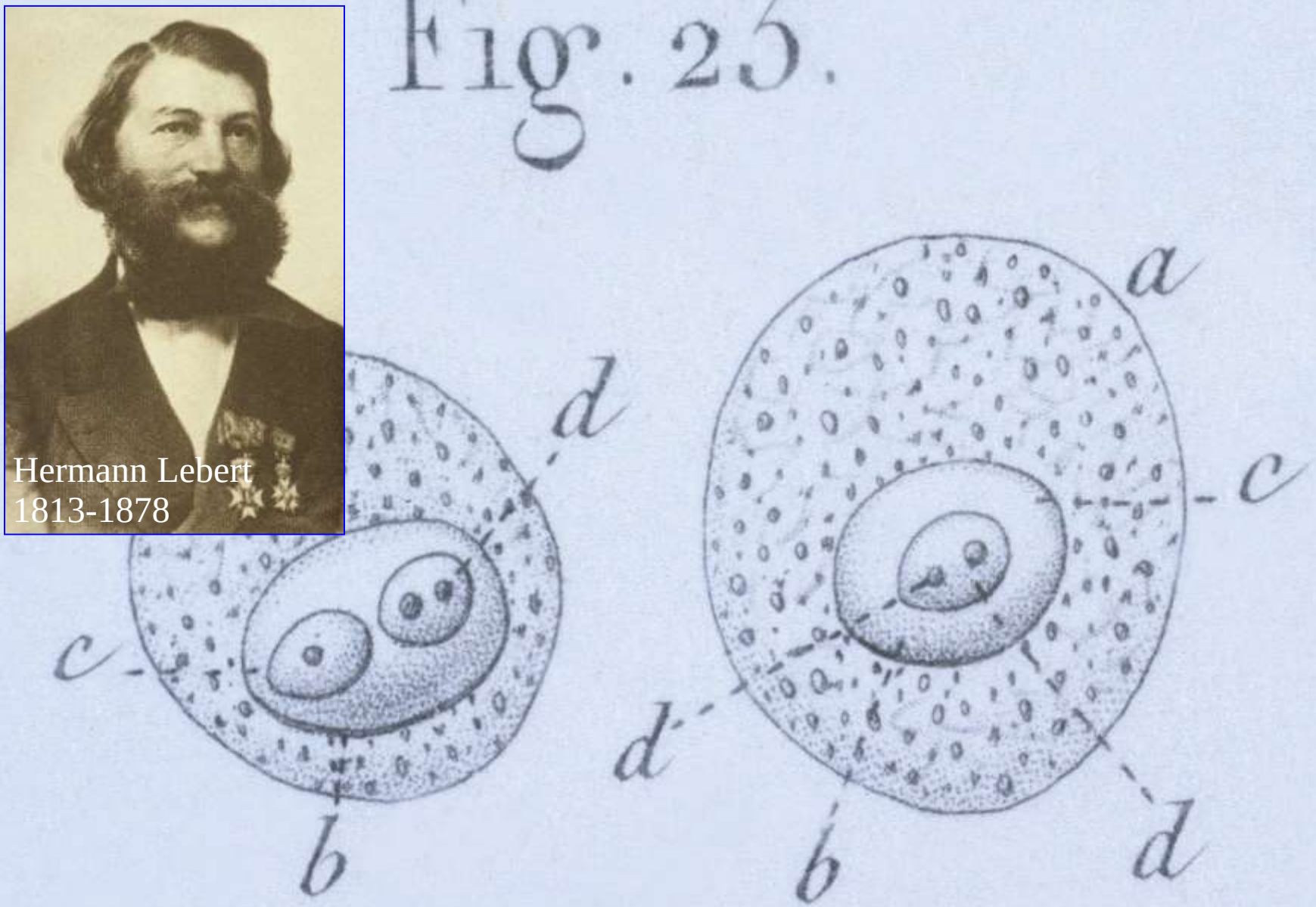
Herausgegeben
VON DEM VEREIN FÜR HEILKUNDE IN PREUSSEN.

1841. Berlin, den 7. Juli. № 27.

I. Ueber die Anzeigen zur Ausrottung krankhafter Geschwülste.

Müller's Untersuchungen begründen nun insofern eine Epoche in der Lehre von den krankhaften Geschwülsten, als durch

Müller's pupil Robert Remak concluded in 1844 that *"cancer, from the outset, tends to develop in a particular way, just as eggs of animals tend to form particular structures, and one cannot believe that a cancerous neoplasm, at its beginning, could develop into anything else. … Every neoplasm already possesses its fundamental properties at its outset, which do not change over time, so that, as a rule, benign neoplasms remain benign and cancerous neoplasms are cancerous from the beginning." "*

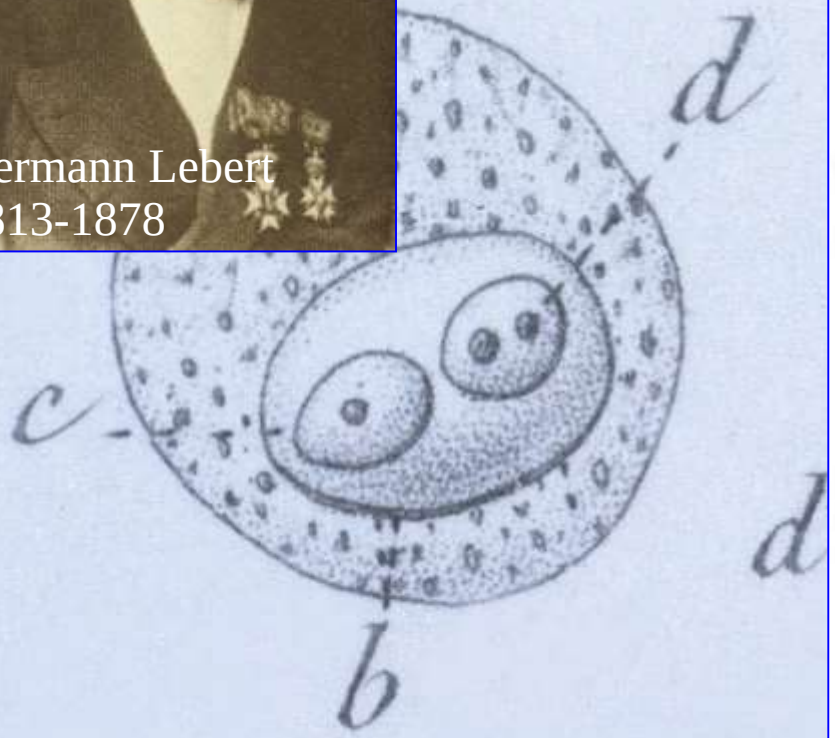


Hermann Lebert
1813-1878

In the 1840s, Hermann Lebert of Paris described nuclear atypia as another typical sign of cancer

Hermann Lebert
1813-1878

Fig. 7



XXXI.

Einige Bemerkungen über die Erkenntniss des Krebses vor der Operation und am Lebenden überhaupt.

Von

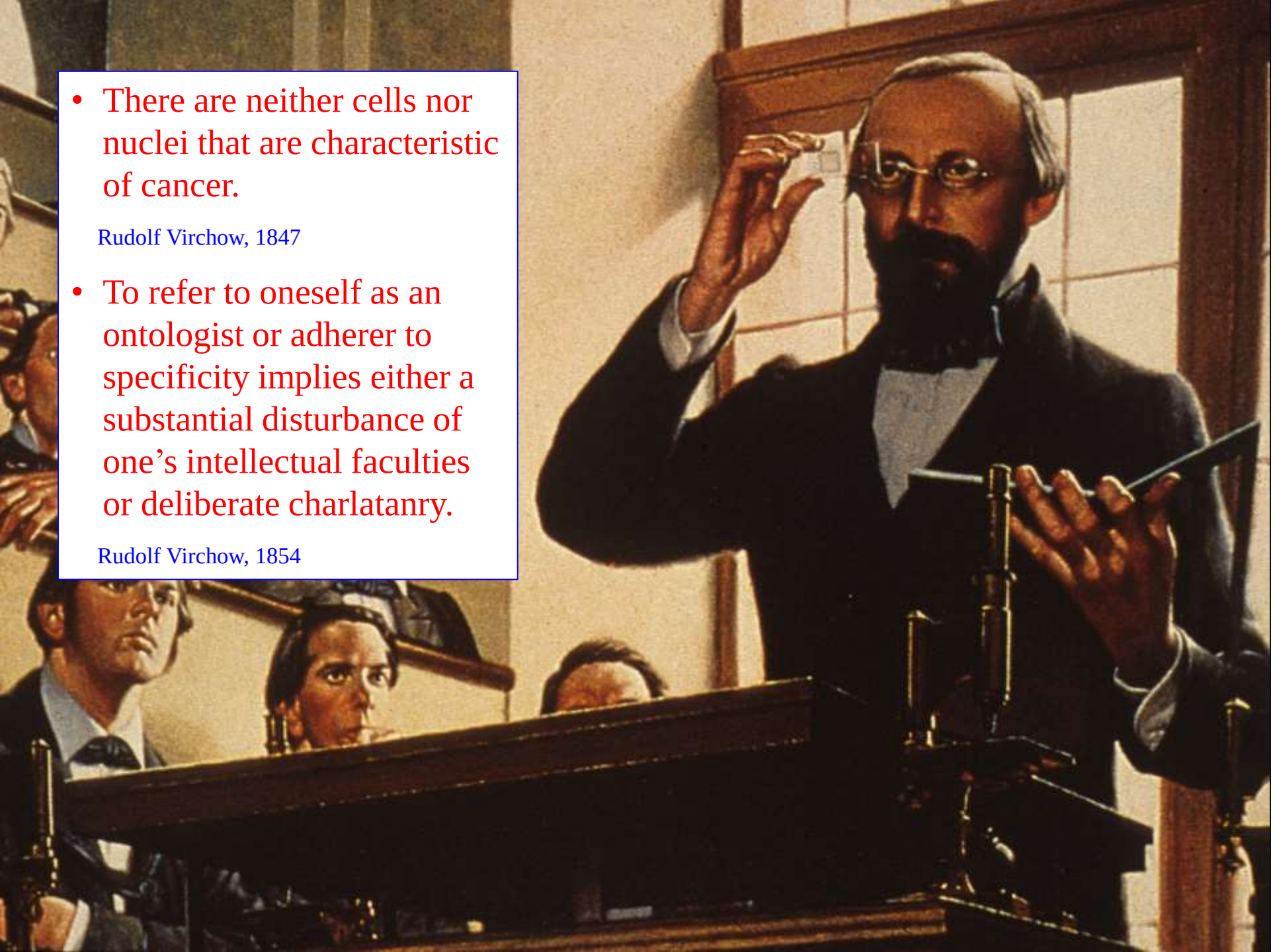
Dr. HERRMANN LEBERT,

praktischem Arzt in Paris.

Es ist in neuerer Zeit vielfach die Frage discutirt worden, ob der Krebs eigenthümliche, durch das Mikroskop wahrnehmbare Elemente besitze. Ich habe mich bereits in meinem Werke über pathologische Physiologie bestimmt für die Specificität der Krebszellen ausgesprochen, aber mit der Einschränkung, dass unter Krebs nicht alles das verstanden würde, was die blinde Routine seit Jahrhunderten als solchen ansieht. So habe ich denn nach Prüfung sämmtlicher pathologischer und anatomischer Charaktere einer grossen Reihe von Geschwülsten vom Krebse so Manches getrennt, was bisher irrig mit demselben verwechselt wurde, worunter namentlich die Geschwülste der Haut zu den meisten Irrungen Anlass gegeben haben. Andererseits habe ich zu beweisen gesucht, dass es nur einen Krebs, so wie nur einen Tuberkel gäbe, und dass die verschiedenen, von den Autoren aufgestellten Species weiter nichts als Formen und Varietäten der gleichen Grundform seien.

Seit der Bekanntmachung meines Werkes, seit also beinahe drei Jahren, habe ich fast ununterbrochen fortgefahren, mich nicht blos mit den feineren Strukturverhältnissen, sondern auch mit der ganzen übrigen Pathologie des Krebses gründlich zu beschäftigen, und wird das Resultat aller dieser Unter-

and proposed the *“specificity of cancer cells.”* In his view, there was only one cancer, and all so-called species of it were *“merely forms and varieties of the same basic form.”*



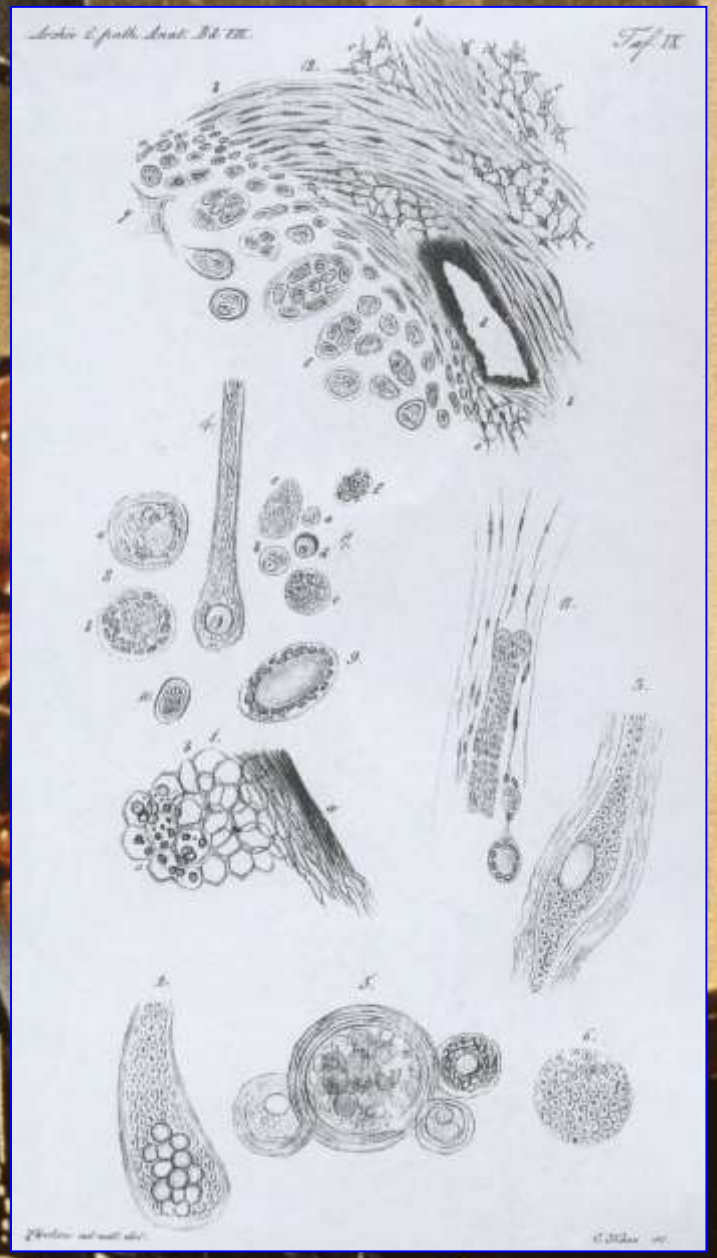
- There are neither cells nor nuclei that are characteristic of cancer.

  Rudolf Virchow, 1847

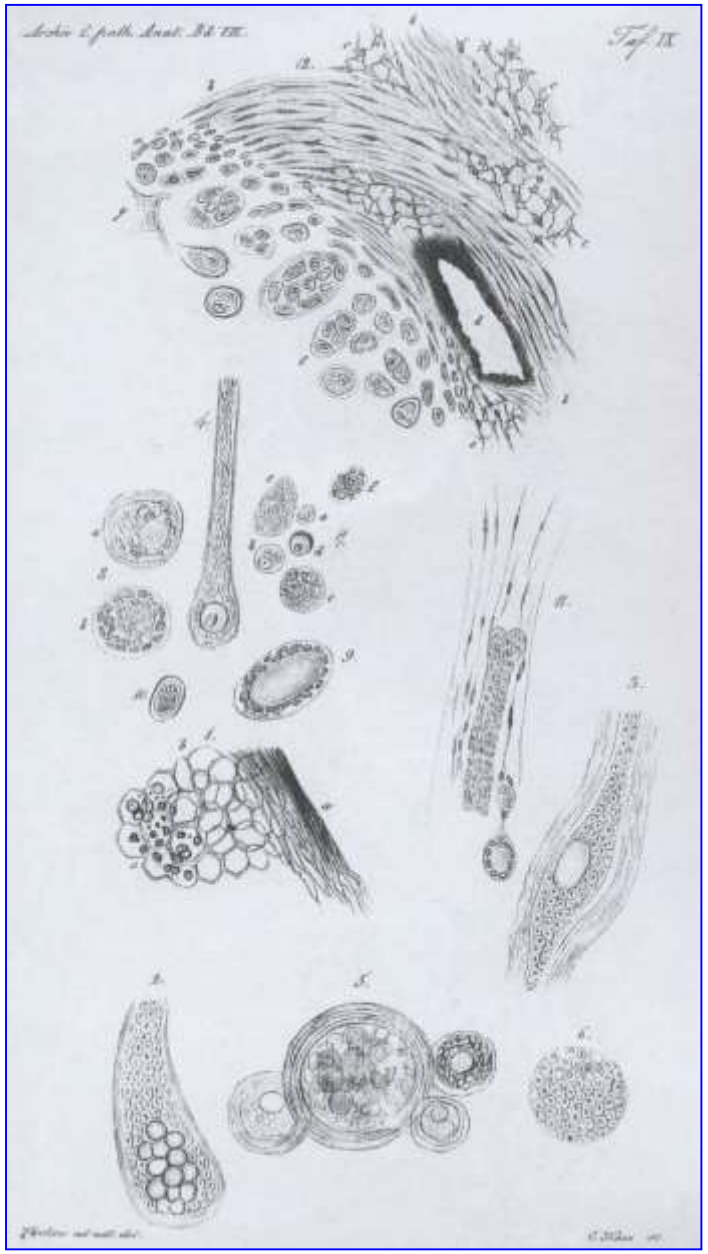
- To refer to oneself as an ontologist or adherer to specificity implies either a substantial disturbance of one's intellectual faculties or deliberate charlatanry.

  Rudolf Virchow, 1854

That claim was criticized harshly by Rudolf Virchow who averred that *"there are neither cells nor nuclei that are characteristic of cancer"* and that, *"to refer to oneself as an ontologist or adherer to specificity, implies either a substantial disturbance of one's intellectual faculties or deliberate charlatanry."*

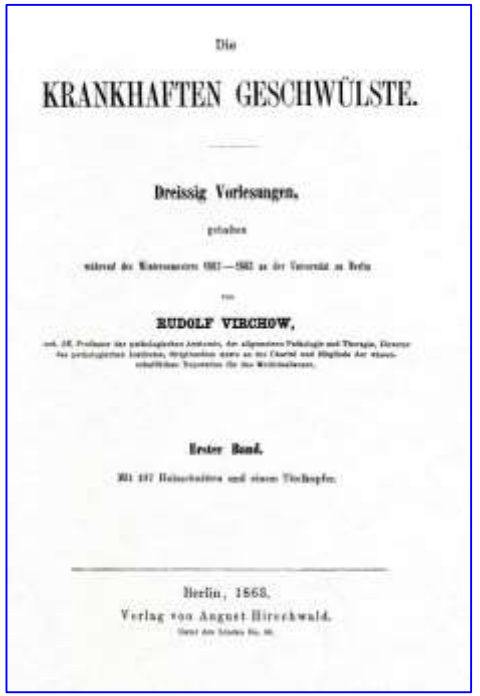


In Virchow's view, there was no fundamental difference between benign and malignant neoplasms. Both resulted from a pathologic stimulus that compromised the tissue, necessitating *"substitution"* of it. In that process, granulation set in, and connective tissue cells differentiated into other types of cells, such as epithelial cells in the case of carcinoma. The behavior of newly formed tissue depended on the degree of deviation from the normal tissue at that site and on the longevity of its cells.



Pathologic neoplasms … are neither benign nor malignant but possess an innocent period and may later become malignant … In regard to this limited malignancy, there is a certain gradation between the different subtypes … that … is not easy to establish. It can only be done according to the grades of malignancy (local infection, dissemination to the neighbourhood, and distant metastases).

Rudolf Virchow, 1863


Die

KRANKHAFTEN GESCHWÜLSTE.

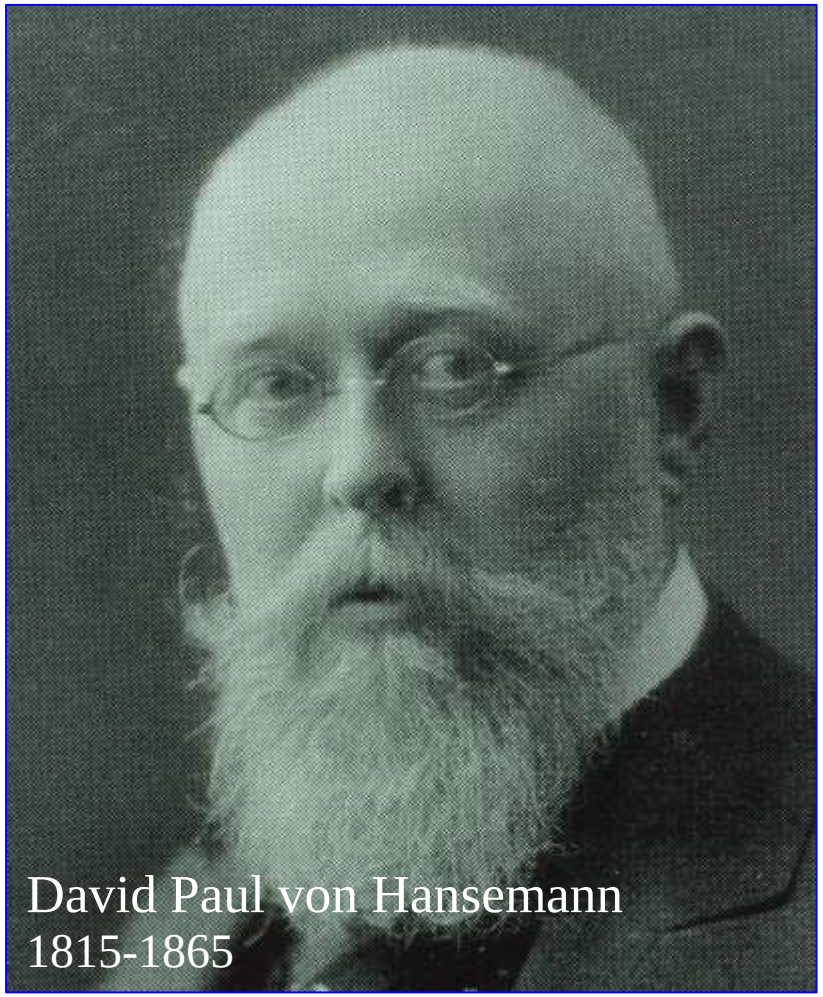
Dreissig Vorlesungen.

RUDOLF VIRCHOW,

Erster Band.

Berlin, 1863.

As stated in his book about "Pathologic neoplasms" in 1863, Virchow believed that, in principle, *"pathologic neoplasms … are neither benign nor malignant but possess an innocent period and may later become malignant … In regard to this limited malignancy, there is a certain gradation between the different subtypes … that … is not easy to establish. It can only be done according to the grades of malignancy (local infection, dissemination to the neighbourhood, and distant metastases)."* In other words, for Virchow, any neoplasm was potentially malignant, and any neoplasm had to be regarded as benign as long as it had not metastasized.

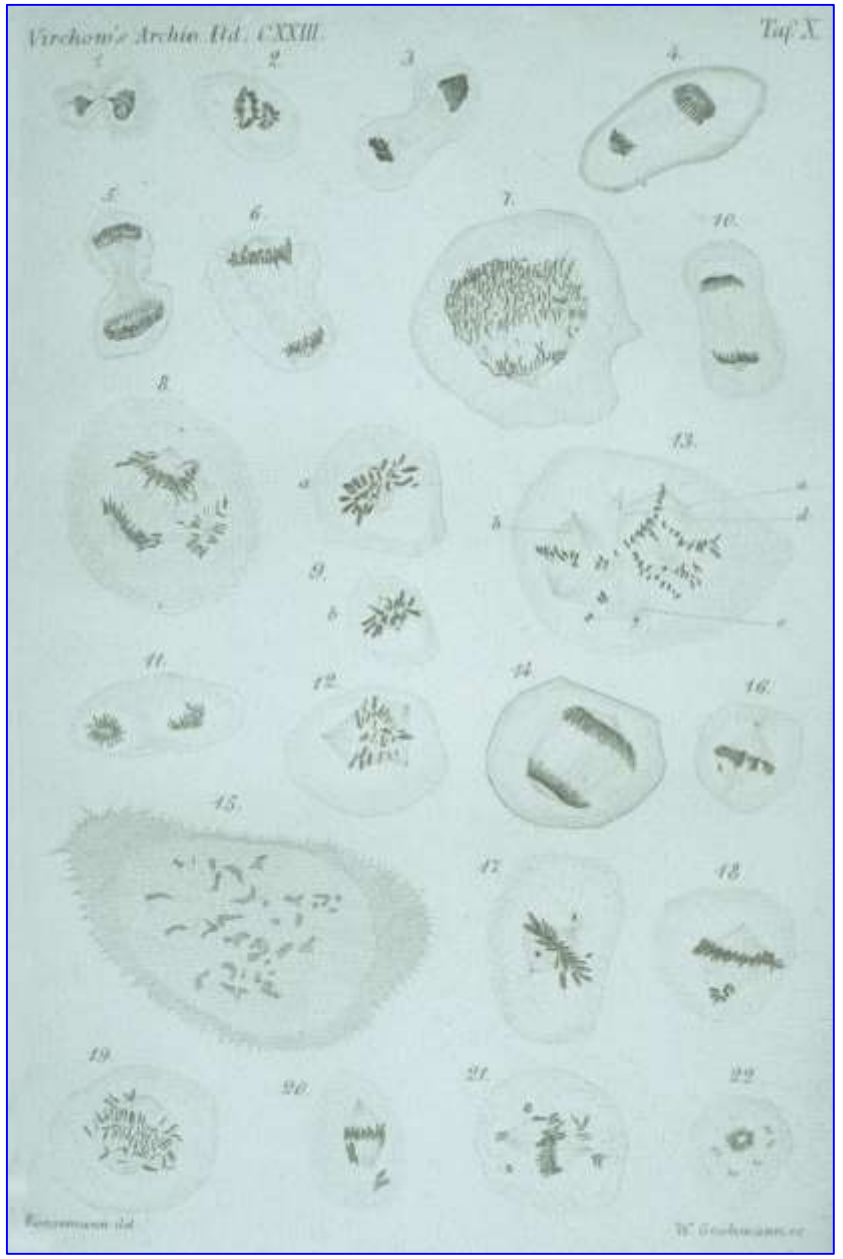


David Paul von Hansemann
1815-1865

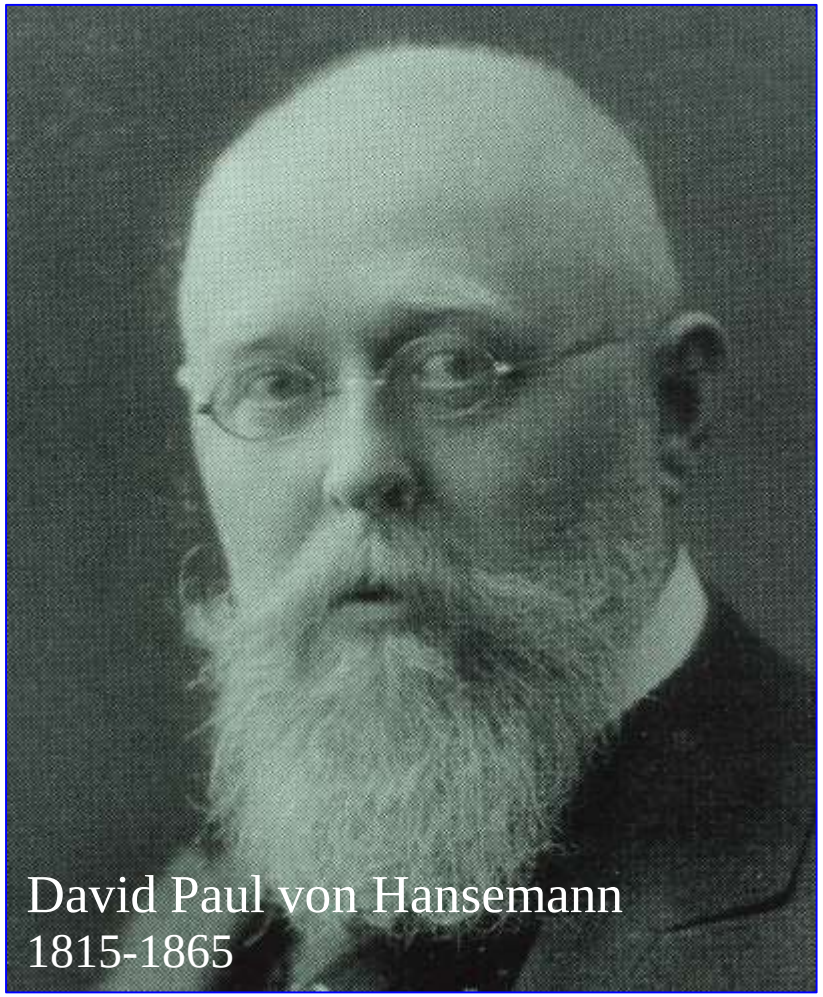
XXIII.

Ueber die Anaplasie der Geschwulstzellen und die asymmetrische Mitose.

Von Dr. David Hansemann,
Privatdocenten und III. anatomischen Assistenten am Pathologischen Institut zu Berlin.



At the end of the 19th century, many of those misconceptions were corrected, especially by one of Virchow's pupils, David Paul von Hansemann. Hansemann found no evidence of a transdifferentiation of tumor cells which favored lineage specificity. Moreover, he noted asymmetrical mitotic figures as a unique feature of malignant neoplasms, leading to aneuploidy and dedifferentiation of neoplastic cells, a phenomenon to which he referred as *"anaplasia."* Hansemann not only attributed the large and hyperchromatic nuclei of cancer cells to that phenomenon



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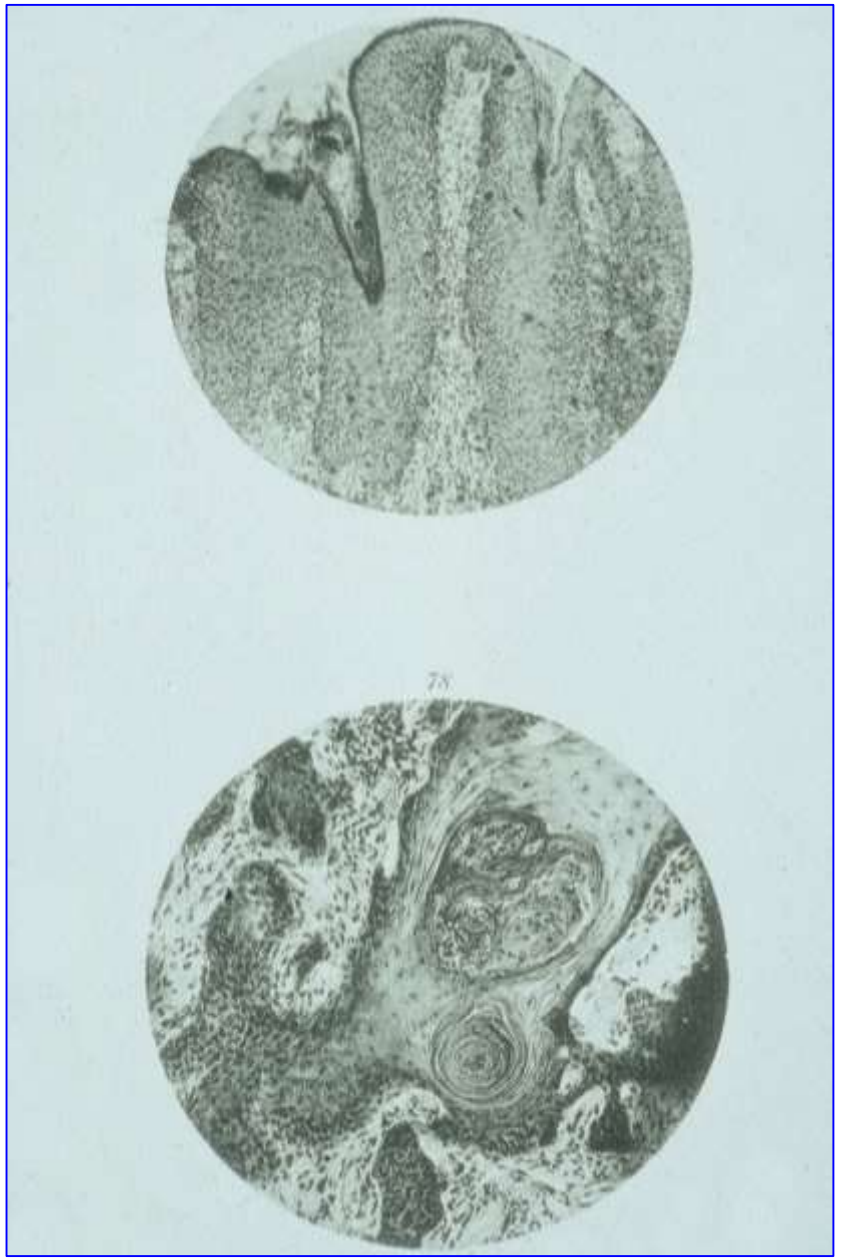


but believed that it was responsible for the formation of cancer, thus supporting Remak's earlier assumption that cancer is malignant from it outset. While Remak, in the 1840s, had depended chiefly on autopsy material, Hansemann 50 years later could examine fresh tissue obtained from the operating room. Moreover, neoplasms were biopsied at a much earlier stage, especially tumors of the skin that were visible and accessible easily.

ON

DISEASE OF THE MAMMARY AREOLA

PRECEDING

CANCER OF THE MAMMARY GLAND.

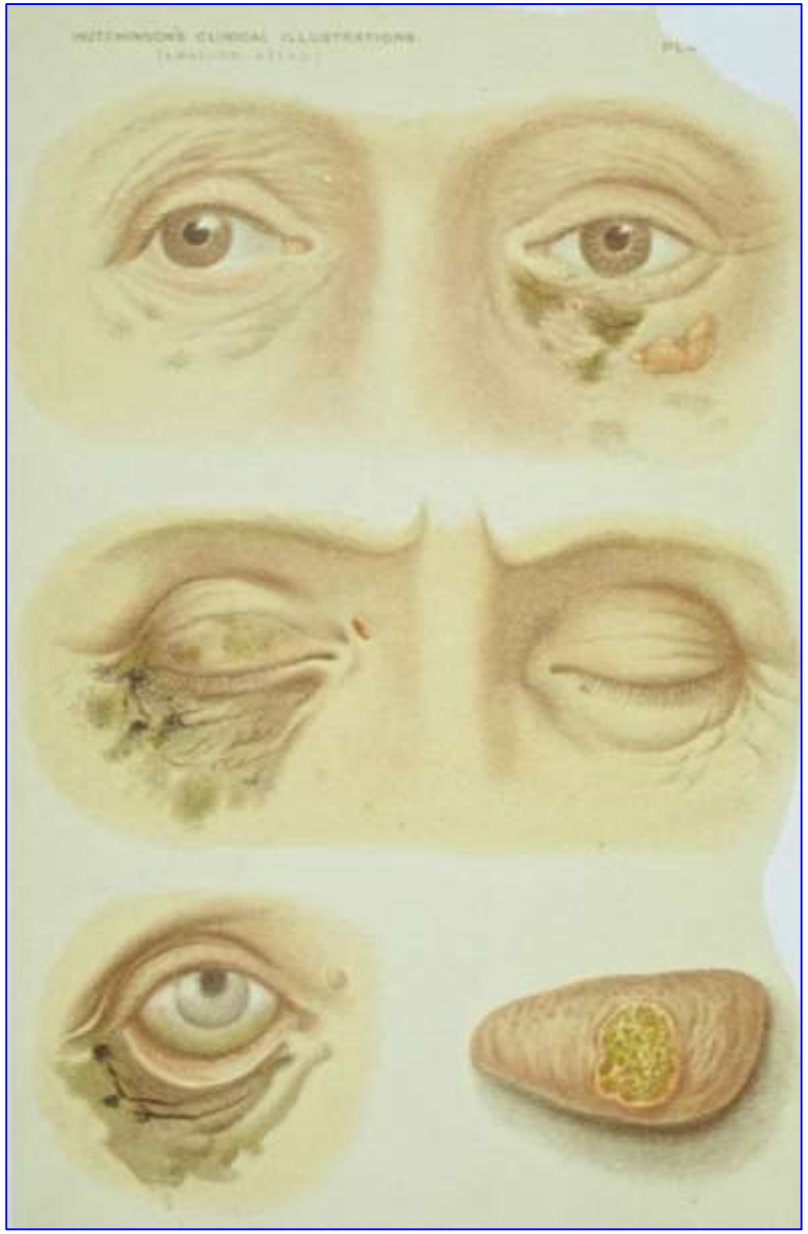
BY

SIR JAMES PAGET, BART., F.R.S.

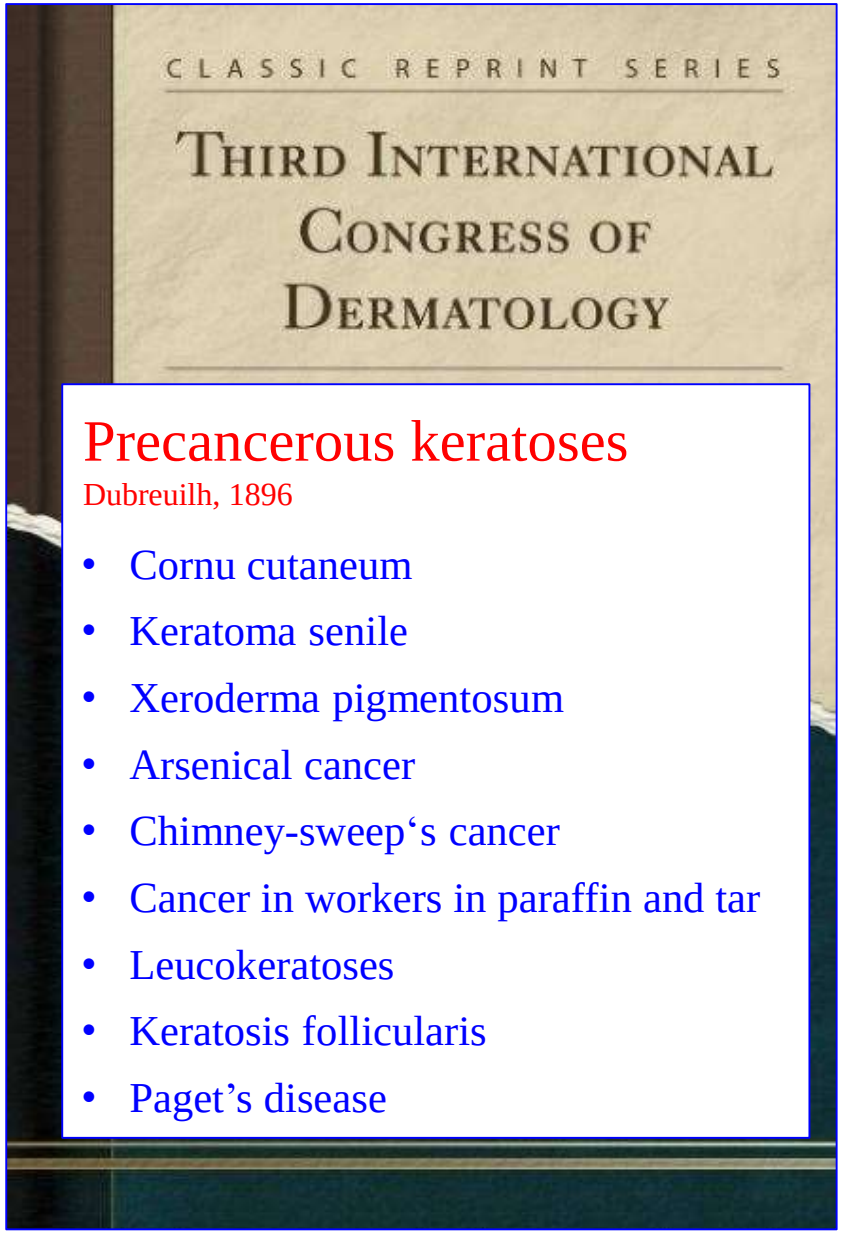
I believe it has not yet been published that certain chronic affections of the skin of the nipple and areola are very often succeeded by the formation of scirrhous cancer in the mammary gland. I have seen about fifteen cases in which this has happened, and the events were in all of them so similar that one description may suffice.

The patients were all women, various in age from 40 to 60 or more years, having in common nothing remarkable but their disease. In all of them the disease began as an eruption on the nipple and areola. In the majority it had the appearance of a florid, intensely red, raw surface, very finely granular, as if nearly the whole thickness of the epidermis were removed; like the surface of very acute diffuse eczema, or like that of an acute balanitis. From such a surface, on the whole or greater part of the nipple and areola, there was always copious, clear, yellowish, viscid exudation. The sensations were commonly tingling, itching, and burning, but the malady was never attended by disturbance of the general health. I have not seen this form of eruption extend beyond the areola, and only once have seen it pass into a deeper ulceration of the skin after the manner of a rodent ulcer.

In some of the cases the eruption has presented the characters of an ordinary chronic eczema, with minute vesications, succeeded



Inevitably, findings suggestive of cancer came to be noticed in tiny lesions that caused no trouble for years, although clear-cut cancer eventually developed in some of them, examples being the “disease of the mammary areola preceding cancer of the mammary gland” described by James Paget or the “melanotic freckle” described by Hutchinson.



Precancerous keratoses

Dubreuilh, 1896

- Cornu cutaneum
- Keratoma senile
- Xeroderma pigmentosum
- Arsenical cancer
- Chimney-sweep‘s cancer
- Cancer in workers in paraffin and tar
- Leucokeratoses
- Keratosis follicularis
- Paget’s disease

William Dubreuilh
1857-1935

Hesitant to use the term “cancer” for such tiny, slow-growing lesions, William Dubreuilh of Bordeaux in 1896 referred to them collectively as “precancerous keratoses” although he was aware that they were not precursors but early stages of the malignant process.

TRAVAUX ORIGINAUX

DE LA MÉLANOSE CIRCONSCRITE PRÉCANCÉREUSE

Par **M. W. Dubreuilh.**

I

Les tumeurs malignes d'origine épithéliale sont très fréquemment précédées et préparées par des lésions d'apparence bénigne qu'on peut appeler lésions précancéreuses ou plus brièvement précancéroses.

Ces lésions peuvent rester indéfiniment stationnaires, elles peuvent même guérir spontanément mais tant qu'elles existent elles sont susceptibles de donner naissance à une néoplasie maligne. Ce n'est pas

When he gave the original description of melanoma in situ under the term "mélanose circonscrite précancereuse" in 1912, Dubreuilh pointed out

TRAVAUX ORIGINAUX

DE LA MÉLANOSE CIRCONSCRITE PRÉCANCÉREUSE

Par **M. W. Dubreuilh.**

Cest n'est pas une transformation maligne, comme on a l'habitude de le dire, c'est seulement une aggravation ou accélération du processus. Car on trouve dans ces précancéroses le caractères essentiels de la tumeur maligne. W. Dubreuilh, 1912

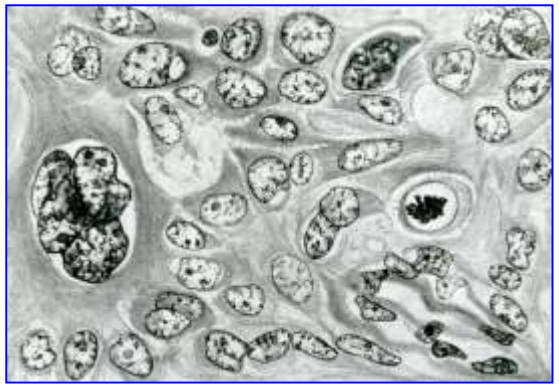
Les ment
précéd peut
appele

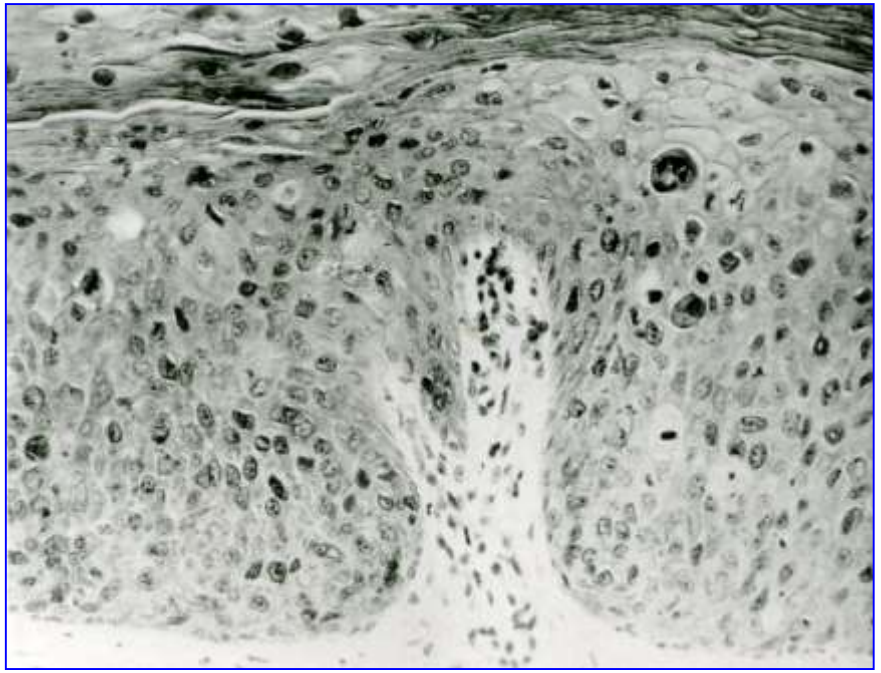
Ces lésions peuvent rester indéfiniment stationnaires, elles peuvent même guérir spontanément mais tant qu'elles existent elles sont susceptibles de donner naissance à une néoplasie maligne. Ce n'est pas

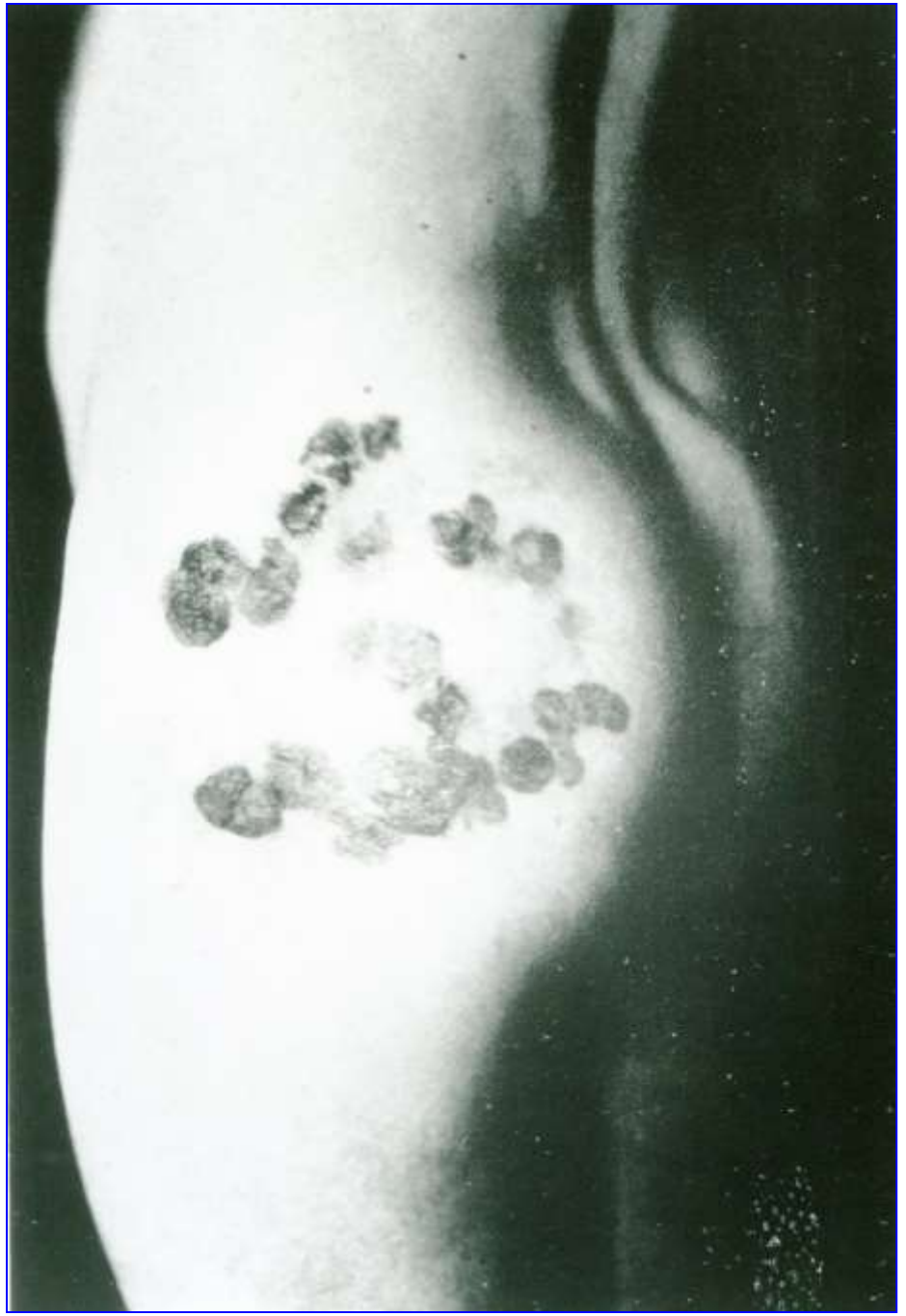
that the development of cancer on those "precanceroses" *"is not a malignant transformation, as one is used to say, but only an aggravation or acceleration of the process. For one finds in these precanceroses the essential elements of the malignant tumor."*

PRECANCEROUS DERMATOSES:
A STUDY OF TWO CASES OF CHRONIC ATYPICAL EPITHELIAL PROLIFERATION.

By John T. Bowen, M.D., Boston.







Four years later, John Templeton Bowen described carcinoma in situ under the name “chronic atypical epithelial proliferation.” Because of slow growth and large dimensions, he refrained from calling the lesions malignant

PRECANCEROUS DERMATOSES:
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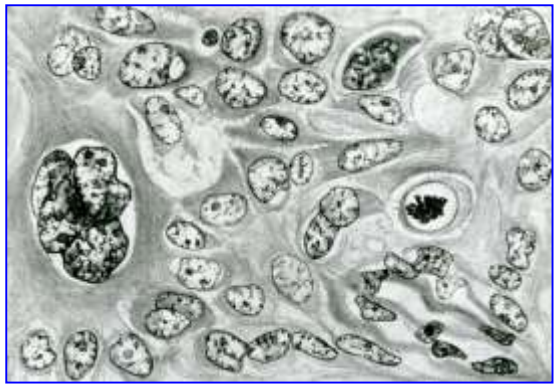
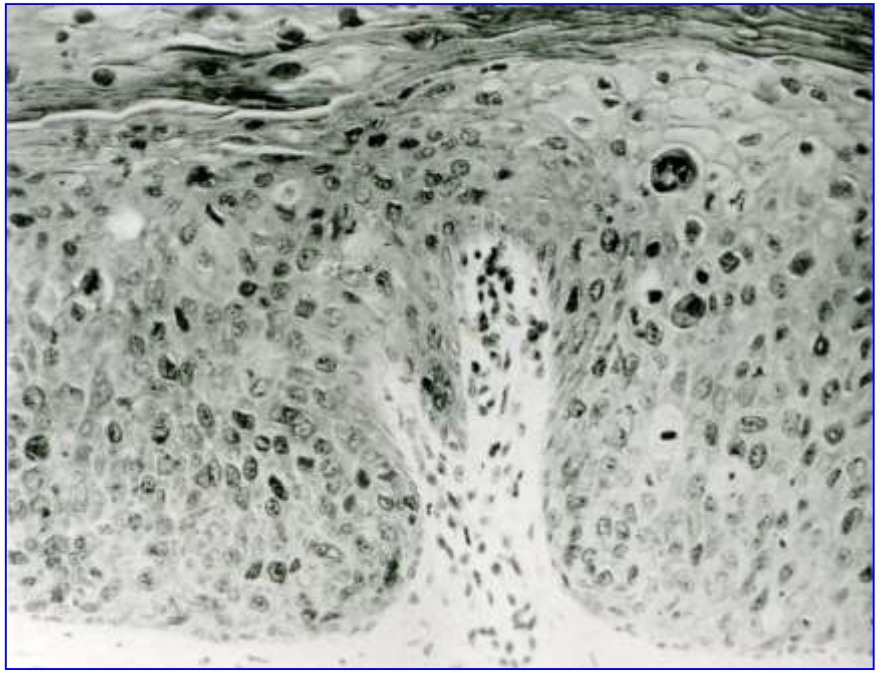
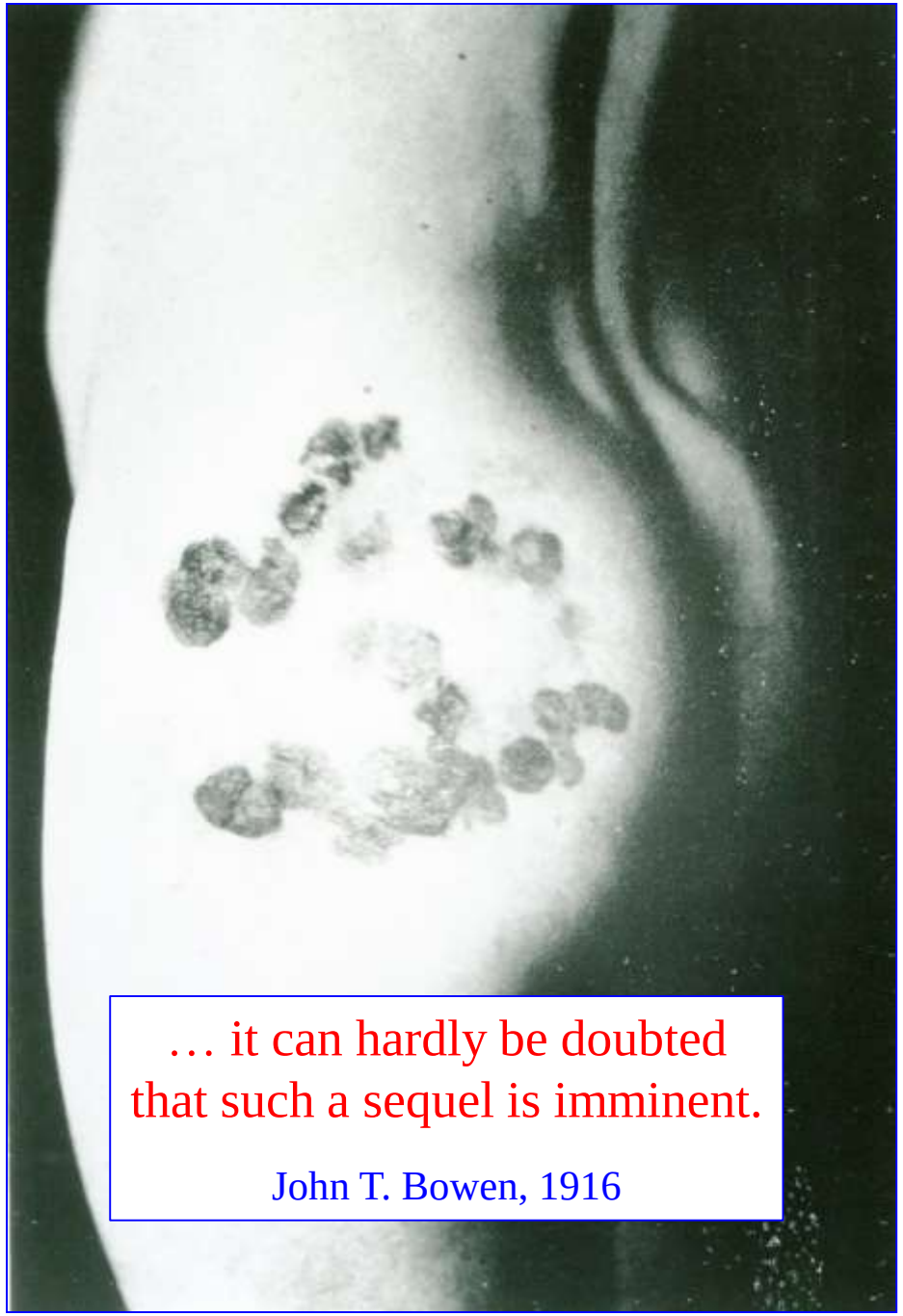






… it can hardly be doubted that such a sequel is imminent.

John T. Bowen, 1916

although he averred that *"it can hardly be doubted that such a sequel is imminent."*

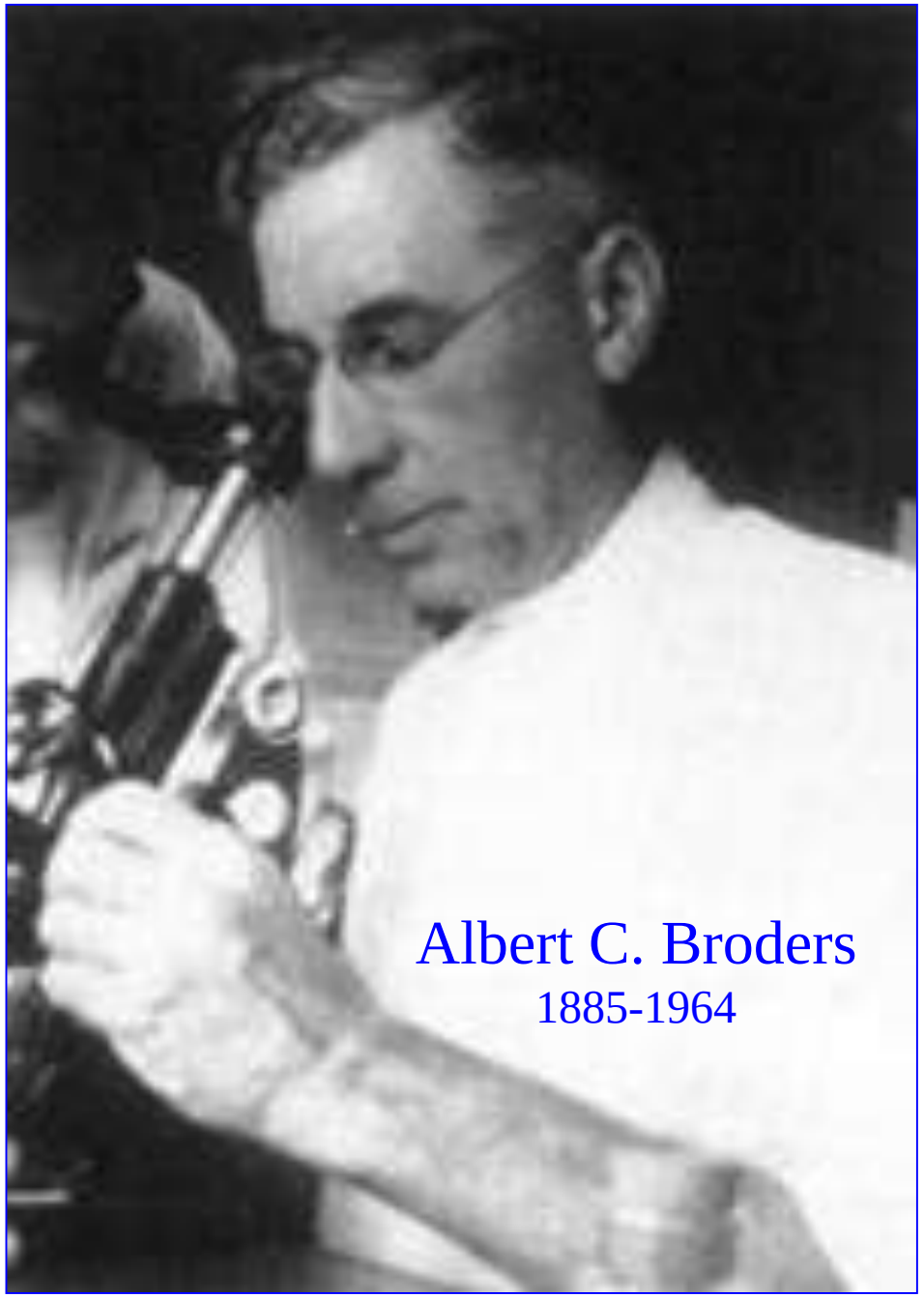
CARCINOMA IN SITU CONTRASTED WITH BENIGN PENETRATING EPITHELIUM

ALBERT C. BRODERS, M.D.
ROCHESTER, MINN.

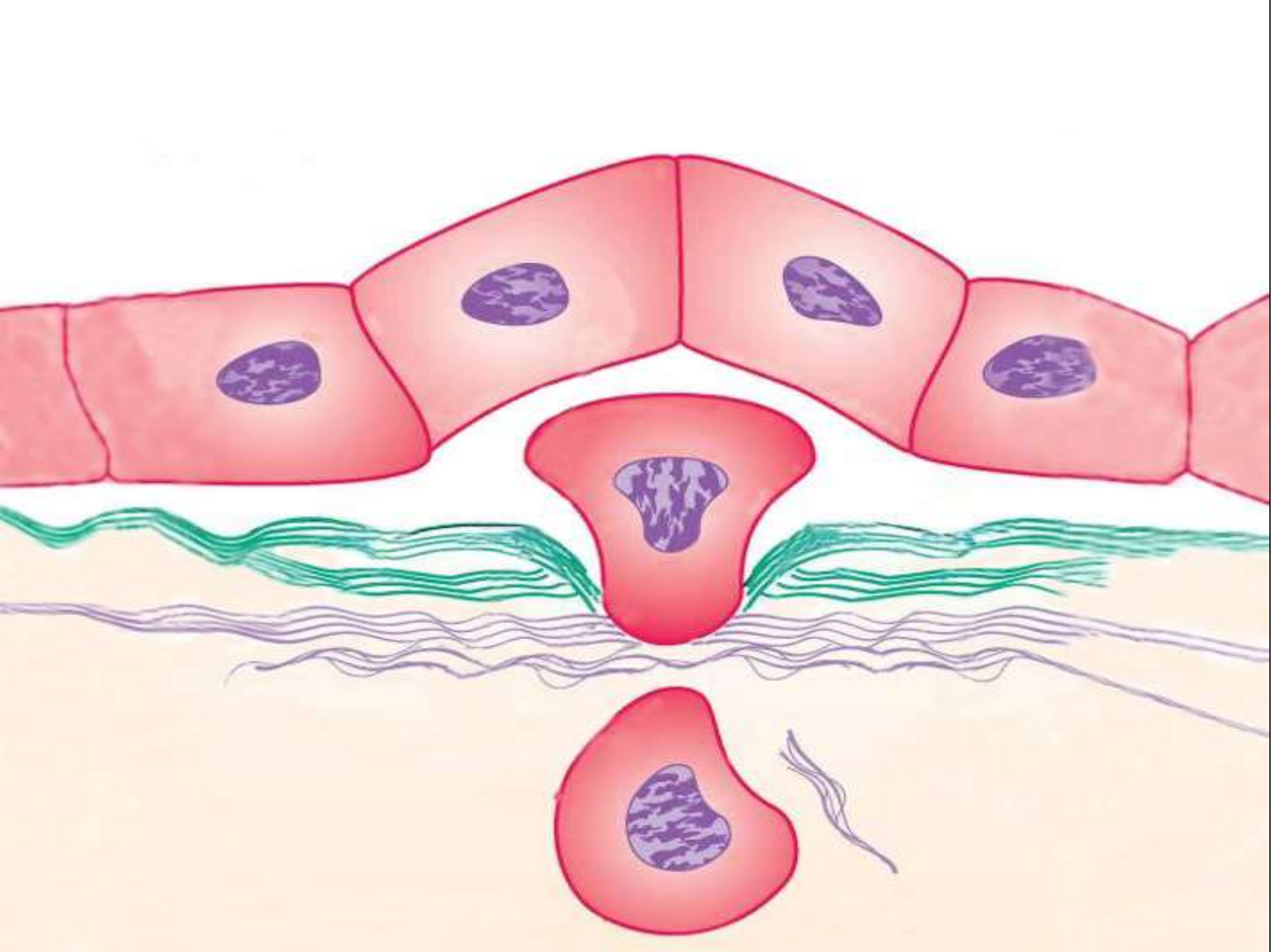
Before I undertake to point out the importance of bringing into the category of carcinoma certain so-called entities that for the most part have remained outside of this category and to exclude from this category epithelial hyperplasia that is not of carcinomatous nature, I believe it is essential to emphasize established facts. These are that the entity called carcinoma or cancer, regardless of etiology, is a primary disease of epithelial cells, and that all other phases and sequelae, although of great importance, are in reality of secondary nature.

The entity called carcinoma or cancer, regardless of etiology, is a primary disease of epithelial cells, and … all other phases or sequelae, although of great importance, are in reality of secondary nature ...

Albert C. Broders, 1932



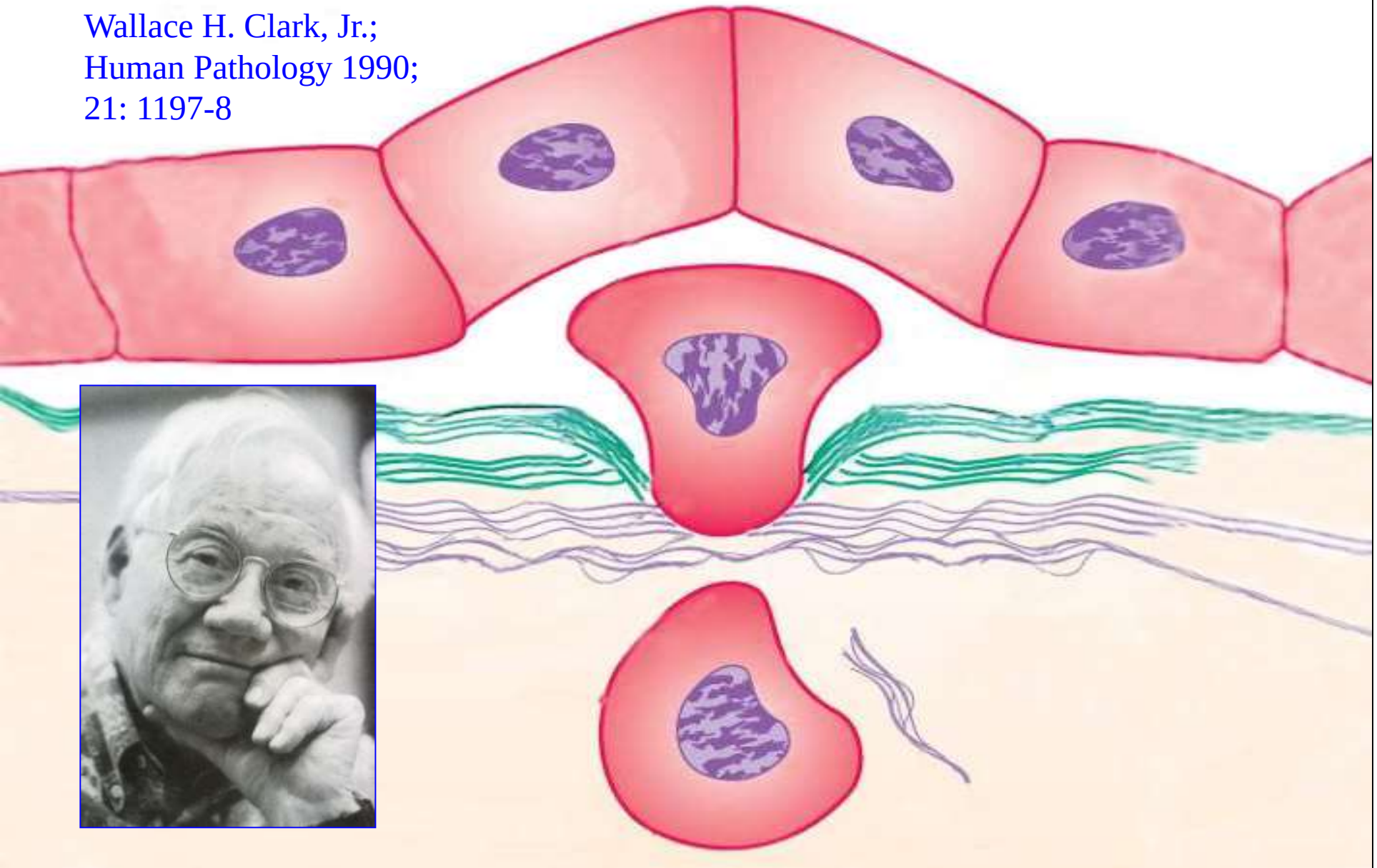
It took 16 more years until Albert Broders coined the term “carcinoma in situ” in order to emphasize the continuity of the malignant process, arguing that *“the entity called carcinoma or cancer, regardless of etiology, is a primary disease of epithelial cells, and … all other phases or sequelae, although of great importance, are in reality of secondary nature.”*



This sounds trivial: whereelse should a neoplasm of epithelial cells arise but within the epithelium? Nonetheless, the continuity of this specific process continues to be denied to this date, a malignant tumor being accepted as an entity only following infiltration of the dermis.

The diagnosis of carcinoma in situ (melanoma in situ, malignancy in situ) is a contradiction in terms, the prototype of an oxymoron.

Wallace H. Clark, Jr.;
Human Pathology 1990;
21: 1197-8



For example, Wallace H. Clark, Jr. declared in 1990 that *"the diagnosis of carcinoma in situ (melanoma in situ, malignancy in situ) is a contradiction in terms, the prototype of an oxymoron."*

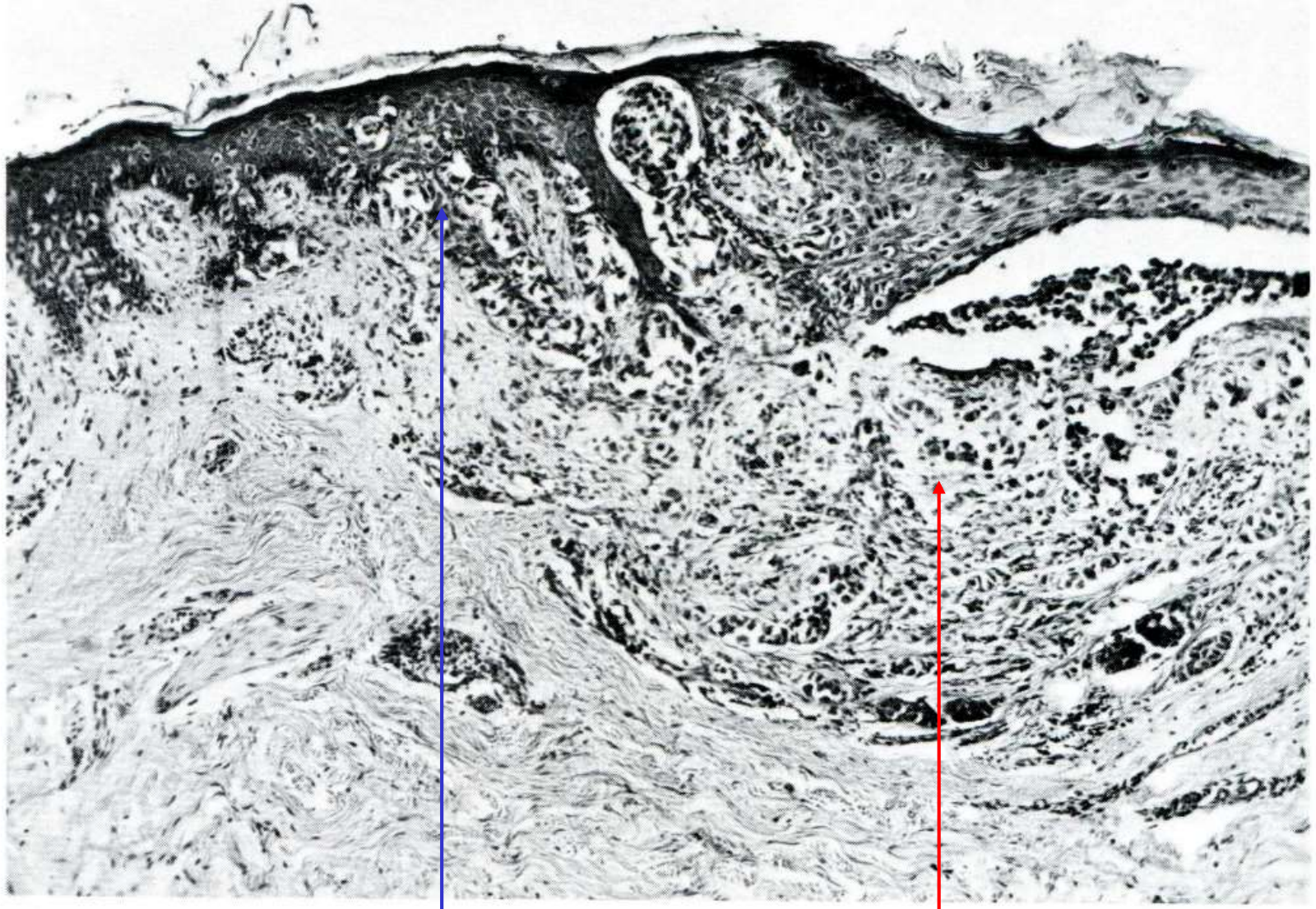


FIGURE 5. On the right, a nodule of atypical melanocytes has formed in a widened papillary dermis and a nest of comparably atypical cells is present at the dermal-epidermal interface. In the latter location, the cells show loss of cohesion. A radial growth component extends into the adjacent epidermis and shows moderate to moderately severe dysplastic changes. The nodule in the papillary dermis qualifies the lesion as an evolving malignant melanoma with thin, level III invasion. The changes in the adjacent epidermis provide a marker for a precursor melanocytic dysplasia.

Even if dealing evidently with the same biologic process, the encroachment of the same cells in the same arangement into the dermis, only the dermal component was accepted as malignant, whereas the intraepidermal one was said to be something biologically different, a “dysplasia.”

A SURVEY OF THE ACTUALITIES AND POTENTIALITIES OF EXFOLIATIVE CYTOLOGY IN CANCER DIAGNOSIS *

By George N. Papanicolaou, M.D., *New York, N. Y.*

In 1925, when for the first time I had occasion to discuss with the late Dr. James Ewing, then Professor of Pathology in our School at Cornell, the possibility of using the vaginal smear as an aid in the diagnosis of uterine cancer, he asked me whether this method could be applied to endometrial as well as to cervical carcinomas. It was his opinion that such a method might prove to be of greater value in the diagnosis of adenocarcinomas of the endometrium than in carcinomas of the cervix, for which everyone would most likely resort to the well established and more dependable method of biopsy.

At that time my knowledge of the cytologic method was very limited and I was in no position to state whether a differential diagnosis between carcinomas of the cervix and adenocarcinomas of the fundus on a cytologic basis was possible. Nor did I know then that the diagnosis of carcinomas of the cervix by the smear method would be possible at an early asymptomatic stage, making it useful in detecting unsuspected lesions, which might still be invisible.

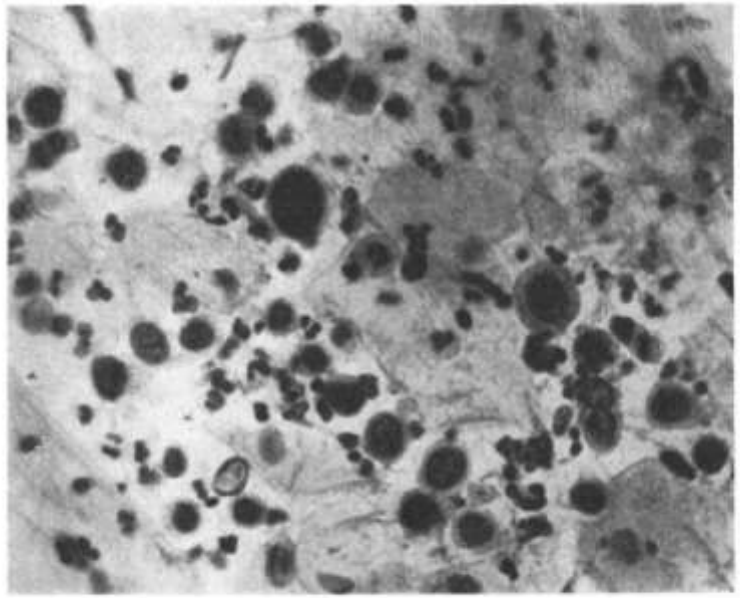


Fig. 3, *b*. Cervical parabasal cells characteristic of parabasal cell dyskaryosis. × 400.

The term “dysplasia’ was proposed to specify such cytologic changes as would be suggestive of but not conclusive for malignancy.

G.N. Papanicolaou,

Ann Intern Med 1949; 31: 661-674.

The term “dysplasia” originally referred to a malformation, but was adopted by Papanicolaou in 1949 in order to refer to slightly atypical cells in cervical smears examined for evidence of cancer. Papanicolaou explained that *“the term ‘dysplasia’ was proposed to specify such cytologic changes as would be suggestive of but not conclusive for malignancy.”* In other words, the term “dysplasia” was a synonym for “I don’t know.”

DYSPLASIA OF THE UTERINE CERVIX

Incidence of Regression, Recurrence, and Cancer

ELIZABETH STERN, M.D.,* AND PETER M. NEELY, PH.D.†

DYSPLASIA OF THE CERVIX IS A LESION THAT is morphologically similar to cancer in

very few were found in the much larger fraction of the population who had not shown
ia. Further, individuals with dysplasia
cervix detected during mass screening
ncer and then kept under observation
uted a high-risk group for cervical
6

Center, University of Chicago, Chicago, Ill.
Received for publication Sept. 24, 1963.

Study of the pattern of variability in a

Carcinoma-in-situ and Dysplasia of the Cervix *

LAMAN A. GRAY, M.D., MALCOLM L. BARNES, M.D., JOSEPH J. LEE, M.D.**

From the Department of Obstetrics and Gynecology, and Department of Pathology, University of Louisville, School of Medicine, and Norton Memorial Infirmary, Louisville, Kentucky

SINCE 1896 atypical changes in the squamous epithelium of the cervix uteri have been noted, and precancerous lesions have been discussed at length.[2] Schottländer and Kermauner[4] in 1912, described surface cancer surrounding invasive squamous cell carcinoma of the cervix as *Oberflächenbelag* or *Randbelag*. Rubin,[6] a student of Schottländer, in 1910, described three cases of incipient carcinoma of the cervix. The first two evidently represented the present day concept of carcinoma-in-situ with gland invasion. Schiller[7] in 1927, described beginning or noninvasive carcinoma of the cervix, and developed his iodine test in 1928 which indicates non-glycogen-containing areas for biopsy. Broders[1] introduced the term *carcinoma-in-situ* in 1932. In 1934, Schiller visited this country and stimulated Novak and many others. In that

rigid criteria
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term *dysplasia*
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OBSTETRICS and GYNECOLOGY Journal of

THE AMERICAN COLLEGE OF OBSTETRICIANS and GYNECOLOGISTS

Volume 38 December 1971 Number 6

Diagnosis and Prognosis of Cervical Dysplasia

UMBERTO VILLA SANTA, MD, FACOG

Although not defined morphologically, it was embraced by pathologists as an astute method to conceal uncertainty and came to be accepted as a diagnosis, the *"diagnosis … of cervical dysplasia."* Of course, "dysplasia" could not be distinguished from incipient carcinoma because it was carcinoma in many cases.

J Clin Pathol 1982;35:1-13

Review article

Cervical intraepithelial neoplasia

CH BUCKLEY, EB BUTLER, H FOX

From the Departments of Pathology, University of Manchester and St Mary's Hospital, Manchester

SUMMARY The theoretical and practical reasons for replacing the terms "cervical dysplasia" and "cervical carcinoma in situ" by the single diagnostic entity of "cervical intraepithelial neoplasia" are reviewed and the advantages and drawbacks of this newer terminology discussed. The histological characteristics and cytological features of the various grades of cervical intraepithelial neoplasia are described and the differential diagnosis of this lesion is considered.

In 1969 Govan and his colleagues gave a detailed account of the classification, nomenclature, histological features, and cytological characteristics of those various abnormalities of cervical squamous epithelium which fall short of a frankly invasive carcinoma.[1] This paper has served well as a guideline, and reference text, for many pathologists and cytologists but in the intervening years our knowledge of cervical pathology has expanded and our understanding and interpretation of cervical epithelial abnormalities has altered. One result of this changing appreciation of cervical lesions has been the introduction of a new terminology: this change has been welcomed by some, but resisted by, and indeed proved unacceptable to, others, with the result that whilst some pathologists and cytologists are currently couching their reports in terms of the new nomenclature others are still using the older and better established terminology. The concurrent use of two systems of nomenclature for cervical lesions is unsatisfactory and prone to cause confusion and misunderstanding.

As advocates of the new system of terminology it is our aim in this paper to detail the conceptual and practical reasons for adopting a new nomenclature, to consider the possible objections to its use, and to redefine the histological and cytological features of abnormalities of the cervical squamous epithelium in terms of this nomenclature.

Nomenclature of cervical epithelial abnormalities

A fundamental division of cervical squamous epithelial abnormalities can be made between those which lack any potential for evolving into an invasive squamous cell carcinoma and those in which there is a significant risk of progression to an invasive neoplasm. The first group of banal changes includes such entities as basal cell hyperplasia, reserve cell hyperplasia, immature squamous metaplasia, and mature squamous metaplasia, all of which are benign, indeed usually physiological, conditions unaccompanied by any increased risk of invasive carcinoma. Epithelial abnormalities that are potentially capable of progression into an invasive neoplasm have traditionally been categorised either as dysplasia or as carcinoma in situ, dysplastic changes within the epithelium being graded as of mild, moderate, or severe degree.

The new nomenclature applies only to those cervical epithelial abnormalities associated with an increased risk of invasive carcinoma, all of which are now put into the single diagnostic category of cervical intraepithelial neoplasia (CIN).[2, 3] Three grades of abnormality are recognised: CIN I which corresponds to mild dysplasia; CIN II which is equivalent to moderate dysplasia; and CIN III which encompasses both severe dysplasia and carcinoma in situ.

REASONS FOR THE CHANGE IN NOMENCLATURE

Firstly, it has to be recognised that there has been, and still is, considerable disagreement as to the definition of both dysplasia and carcinoma in situ. Thus in 1961, an International Committee on Histological Terminology defined a carcinoma in situ as "a lesion of the epithelium in which, throughout its thickness, no differentiation takes place."[4] This was also the view taken by Govan *et al* who insisted upon complete loss of stratification and of cellular differentiation as defining criteria.[1] There is no doubt that most histopathologists accept, and rely on, this definition but Burghardt[5] has maintained that there can be no theoretical objection to the concept of a differentiated carcinoma in situ, defining this

Accepted for publication 20 July 1981

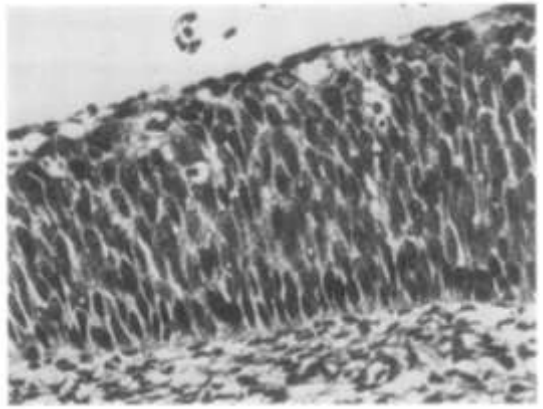


Fig. 3 CIN III: undifferentiated cells of basaloid type occupy almost the full thickness of the epithelium. The constituent cells in this example are somewhat spindle-shaped. Haematoxylin and eosin × 350.

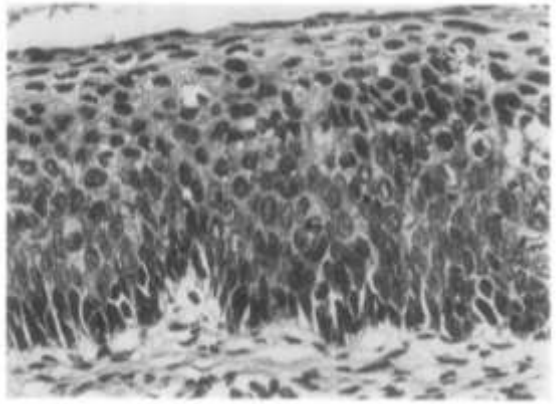


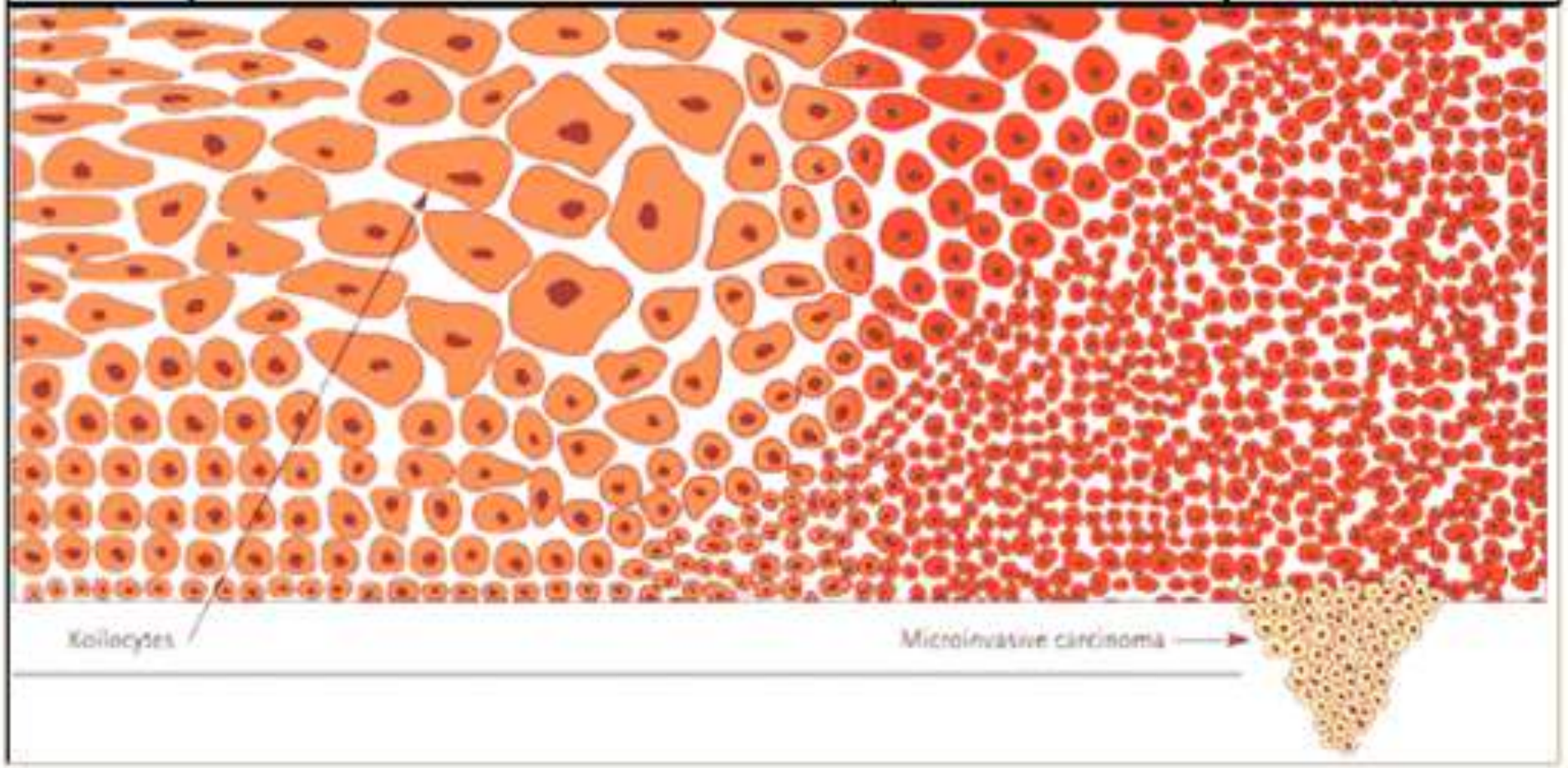
Fig. 2 Squamous epithelium showing CIN II. Undifferentiated cells occupy less than two-thirds of the epithelial structure. Haematoxylin and eosin × 350.

All cases of "dysplasia" …, irrespective of grade, [belong to] a spectrum of intraepithelial change which begins as a generally well differentiated neoplasm … and ends with invasive carcinoma.

The identity led to the introduction of a new term, "cervical intraepithelial neoplasia," that was meant to replace *"the terms 'cervical dysplasia' and 'cervical carcinoma in situ' by a single diagnostic entity."* Its proponents emphasized that *"all cases of "dysplasia …, irrespective of grade, [belong to] a spectrum of intraepithelial change which begins as a generally well differentiated neoplasm … and ends with invasive carcinoma,"* but instead of giving a diagnosis in the language of clinical medicine and acknowledging uncertainty in equivocal cases, they resorted to yet another non-specific histopathologic designation.

Schematic Representation of SIL

	Low-grade squamous intraepithelial lesion (LSIL)		High-grade squamous intraepithelial lesion (HSIL)	
	Condyloma	CIN/AIN grade 1	CIN/AIN grade 2	CIN/AIN grade 3
Normal	Very mild to mild dysplasia		Moderate dysplasia	Severe dysplasia / *In Situ* carcinoma



The same is true for other terms introduced subsequently, such as the latest invention, “squamous intraepithelial lesion,” that is applied indiscriminately to benign and malignant lesions, from condyloma to in-situ carcinoma. This is not history any more, this is current.

Prostate Cancer

High-Grade Prostatic Intraepithelial Neoplasia on a Prostate Biopsy—What Does It Mean?

Reviewed by Alan W. Partin, MD, PhD

Department of Urology, Johns Hopkins University School of Medicine, Baltimore, MD

[*Rev Urol.* 2002;4(3):157–158]

WJGP *World Journal of Gastrointestinal Pathophysiology*

Online Submissions: http://www.wjgnet.com/2150-5330office
wjgp@wjgnet.com
doi:10.4291/wjgp.v2.i6.93

World J Gastrointest Pathophysiol 2011 December 15; 2(6): 93-99
ISSN 2150-5330 (online)

EDITORIAL

Treatment strategy for gastric non-invasive intraepithelial neoplasia diagnosed by endoscopic biopsy

Tsutomu Nishida, Shusaku Tsutsui, Motohiko Kato, Takuya Inoue, Shunsuke Yamamoto, Yoshito Hayashi,

Aneuploidy and proliferation in keratinocytic intraepidermal neoplasias

Tim Smits[1], Diana Olthuis[1], Willeke A. M. Blokx[2], Marloes M. Kleinpenning[1], Peter C. M. van de Kerkhof[1] Piet E. J. van Erp[1] and Marie-Jeanne P. Gerritsen[1]

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The Netherlands, Tel.: +31 24 3613724, Fax: +31 24 3541184, e-mail: t.smits@derma.umcn.nl

Accepted for publication 8 September 2006

Abstract: Cutaneous squamous (pre)malignancies can be classified according to the keratinocytic intraepidermal neoplasia (KIN) classification. Aneuploidy can be seen as the result of chromosomal aberrations leading to altered DNA content and has been strongly associated with malignancy. Hyperproliferation is also strongly associated with tumorigenesis. The aim of the study was to analyse the presence and the amount of aneuploidy and proliferation in the progression from intraepithelial neoplasm to microinvasive carcinoma (miSCC). For this purpose, nuclei were isolated from 116 formalin-fixed KIN lesions from 68 patients in which DNA content was measured by flow cytometry. Proliferation was assessed by immunohistochemical staining for Ki67 as well as by flow cytometry. Aneuploidy was increasingly found in higher KIN lesions, but not in normal skin. However, in miSCC aneuploidy was relatively less frequently found. DN indices (mean ± SE) of KIN III-lesions (1.57 ± 0.05) were significantly lower compared with KIN I/II lesions (1.71 ± Ki67 expression was strongly positively correlated with KIN and proved to be a good adjunct in the classification of KI Thus, aneuploidy occurred more frequently in higher KIN indicating cumulative damage during KIN progression. Th frequency of aneuploidy in miSCC compared with KIN III point at alternative routes towards invasive carcinoma besi serial progression through all three KIN stages. Ki67 expres appears a valuable marker in the classification of KINs.

Key words: actinic keratosis – aneuploidy – Bowen's disea KIN – proliferation

Please cite this paper as: Aneuploidy and proliferation in keratinocytic intraepidermal neoplasias. Experimental Dermatology 2007; 16: 81–86.

The American Journal of Dermatopathology 9(1): 80–82, 1987

Letters to the Editor

Intraepithelial Melanocytic Neoplasia: A Classification by Pattern Analysis of Proliferations of Atypical Melanocytes

To the Editor:

The difficulty in classifying intraepithelial proliferations of atypical melanocytes is reflected in the confusing array of diagnostic terms used to describe them. When experts use names like atypical melanocytic hyperplasia, melanocytic dysplasia, active junctional nevus, and melanoma in situ, not only do they mean different things, but they often cannot agree on specific diagnoses (i.e., melanocytic nevi or malignant melanomas) (1).

Suggestions have been made for better methods of classification (2), but they have not included specific criteria for diagnosis. I propose here a simple classification for intraepithelial melanocytic proliferations of atypical melanocytes using pattern analysis, analogous to that already in use for cervical neoplasia, namely, intraepithelial melanocytic neoplasia (IMN).

This classification does not imply all malignant melanomas must progress from IMN-I through IMN-III in preparation for descent into the dermis, although this may often be the case. IMN-I, IMN-II, and IMN-III should be treated by simple conservative adequate excisions.

Dermatologists and pathologists are urged to adopt this classification because: (a) It is easy to use; (b) it avoids imprecise terms like "melanocytic dysplasia," "active junctional nevus," and "atypical melanocytic hyperplasia"; (c) it enables circumvention of the term "melanoma in situ," yet communicates the same information (i.e., IMN-III).

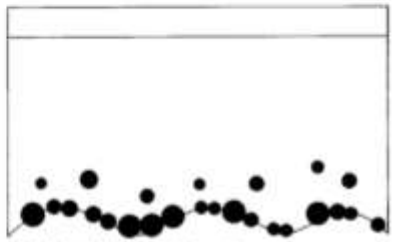


FIG. 2. In IMN-II, atypical melanocytes are present singly and in nests at the dermal–epidermal junction and within the lower one-third of the epithelium.

Regrettably, the language of gynecopathology has infected other fields of pathology, including dermatopathology, with terms such as "keratinocytic intraepidermal neoplasia" and "intraepithelial melanocytic neoplasia" being proposed as diagnoses. This triumph of a non-specific nomenclature can be attributed to two chief factors. First, controversies about diagnoses can be ommitted. Things are much easier for pathologists if they are not forced to decide whether a given proliferation is a condyloma or an incipient carcinoma, an unusual nevus or a melanoma.

The American Journal of Dermatopathology
Volume 6 Supplement 1
Summer 1984

CONTROVERSIES IN DERMATOPATHOLOGY

CONTROVERSY 1: CAN HISTOPATHOLOGISTS DIAGNOSE MALIGNANT MELANOMA *IN SITU* CORRECTLY AND CONSISTENTLY?

Malignant melanoma *in situ*, precancerous melanosis, or atypical intraepidermal melanocytic proliferation

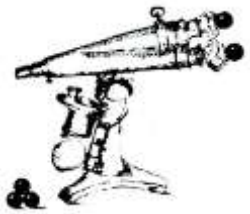
Arkadi M. Rywlin, M.D.

This simplification has led to much greater diagnostic consistency.

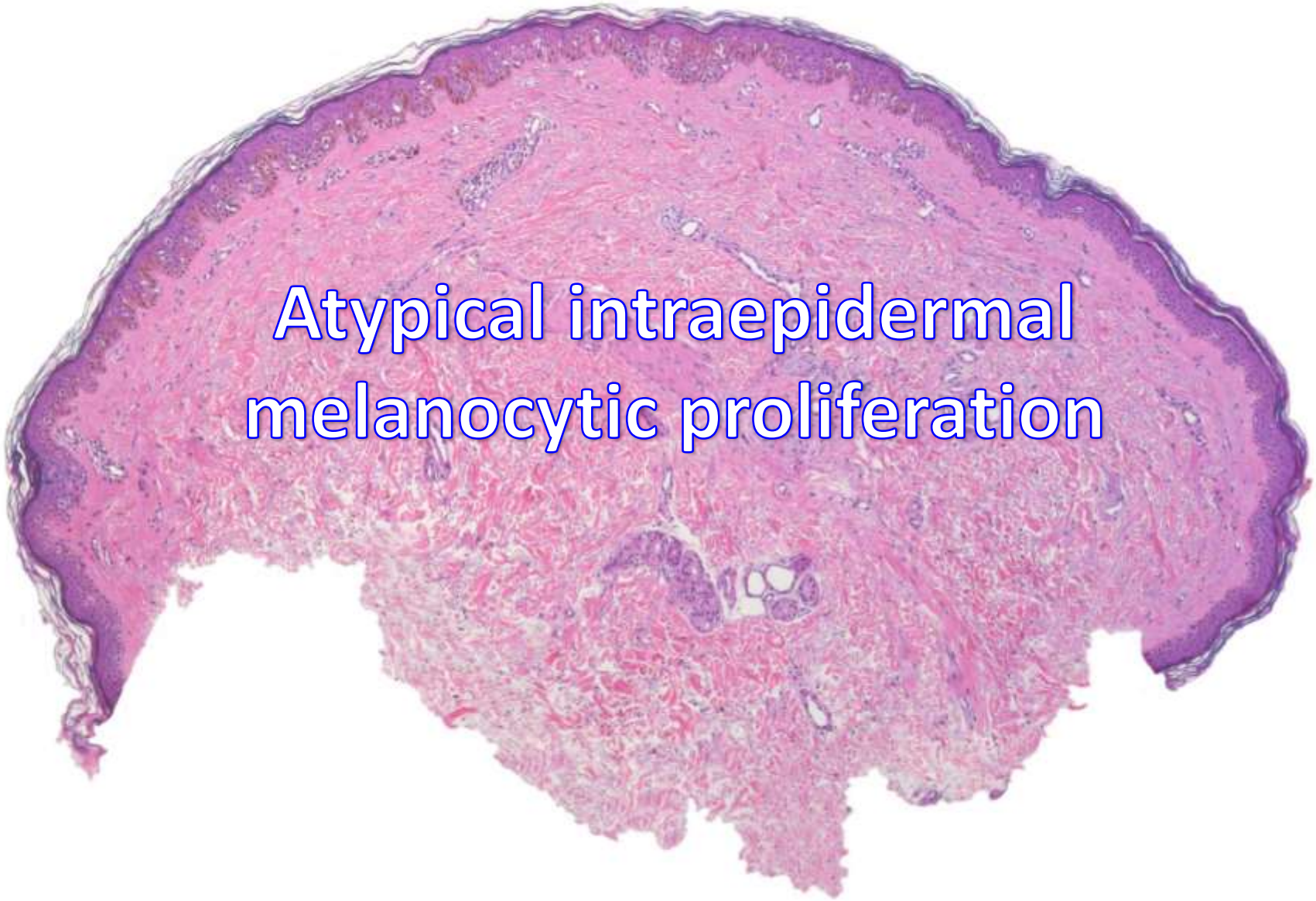
Arkadi M. Rywlin, 1984

When American pathologist Arkadi Rywlin plead for the use of the term “atypical intraepidermal melanocytic proliferation,” in lieu of “melanoma in situ,” he argued that *“this simplification has led to much greater diagnostic consistency,”* and he was right. By such non-committal terms, consistency among pathologists can be improved, but only through relinquishment of a diagnosis. If one refers to nevi and melanomas by the same name,

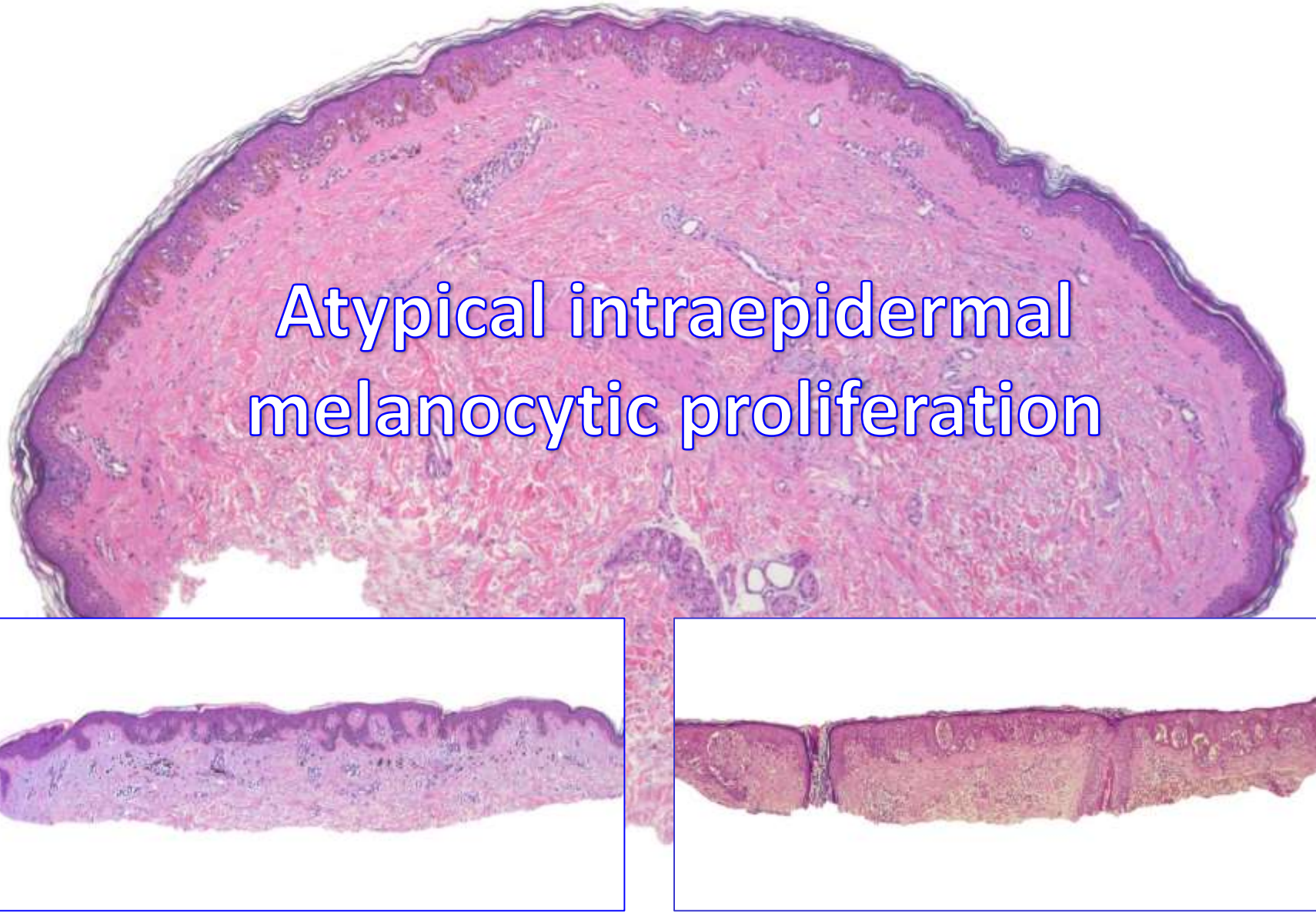
Pathology Report



one could just as well submit a blank page as a pathology report; in that case, there would be even less discordance. A diagnosis, however, is the raison d'être of histopathology.



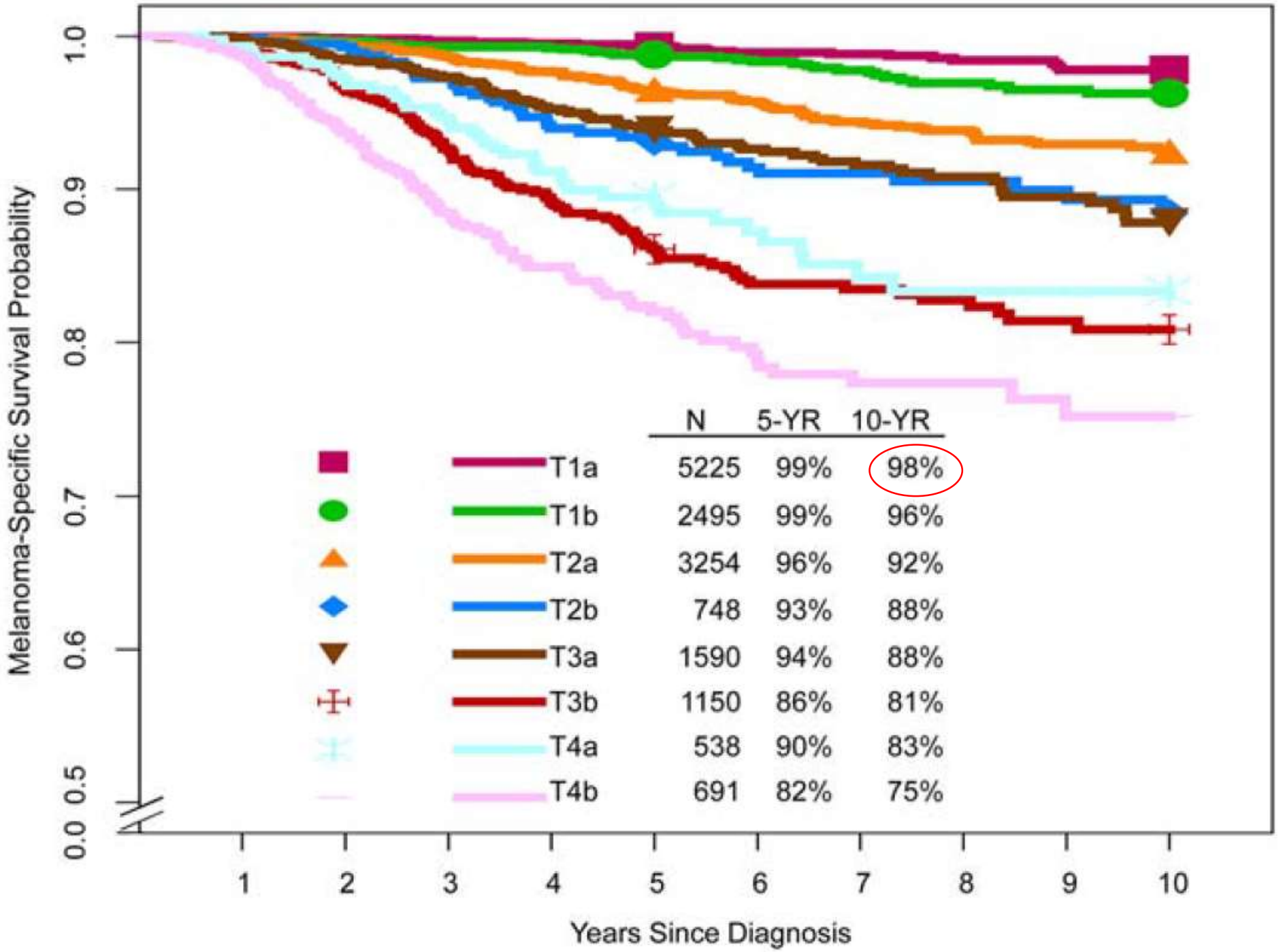
It may be difficult and controversial, but if designations such as “atypical intraepidermal melanocytic proliferation” are accepted, specific diagnoses are no longer sought. Moreover, this term is used not only for challenging cases



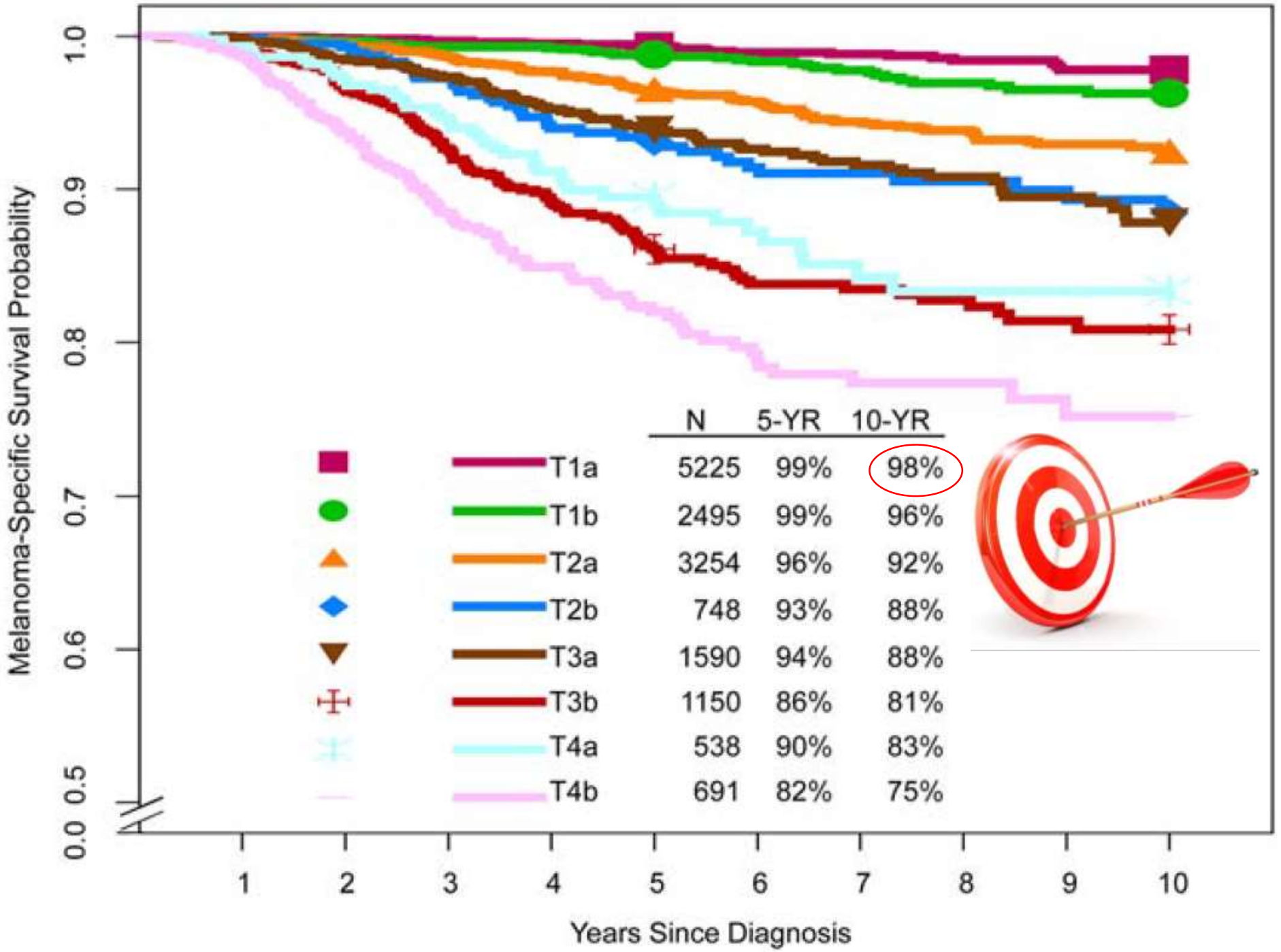
but also for clear-cut nevi and clear-cut melanomas.

The second reason for the triumph of non-specific designations in oncology is their indeterminacy. A diagnosis is expected to be correct,

and any mistake can have legal repercussions. With a term that leaves all possibilities open, pathologists remain on the safe side. That is why statements concerning prognosis are so attractive: they are always right.



For example, according to the current AJCC melanoma classification, melanomas in stage T1a have a 10-year survival rate of 98%. If the patient survives, this is the expected outcome; if he dies, he belongs to the unhappy 2%,



but the prediction was on target. One cannot err with prognosis.

Hence, non-specific designations supplemented with a remark about prognosis are becoming more and more popular.

Addressing overdiagnosis and overtreatment in cancer: a prescription for change

Laura J Esserman, Ian M Thompson, Brian Reid, Peter Nelson, David F Ransohoff, H Gilbert Welch, Shelley Hwang, Donald A Berry, Kenneth W Kinzler, William C Black, Mina Bissell, Howard Parnes, Sudhir Srivastava

A vast range of disorders—from indolent to fast-growing lesions—are labelled as cancer. Therefore, we believe that several changes should be made to the approach to cancer screening and care, such as use of new terminology for indolent and precancerous disorders. We propose the term indolent lesion of epithelial origin, or IDLE, for those lesions (currently labelled as cancers) and their precursors that are unlikely to cause harm if they are left untreated. Furthermore, precursors of cancer or high-risk disorders should not have the term cancer in them. The rationale for this change in approach is that indolent lesions with low malignant potential are common, and screening brings indolent lesions and their precursors to clinical attention, which leads to overdiagnosis and, if unrecognised, possible overtreatment. To minimise that potential, new strategies should be adopted to better define and manage IDLEs. Screening guidelines should be revised to lower the chance of detection of minimal-risk IDLEs and inconsequential cancers with the same energy traditionally used to increase the sensitivity of screening tests. Changing the terminology for some of the lesions currently referred to as cancer will allow physicians to shift medicolegal notions and perceived risk to reflect the evolving understanding of biology, be more judicious about when a biopsy should be done, and organise studies and registries that offer observation or less invasive approaches for indolent disease. Emphasis on avoidance of harm while assuring benefit will improve screening and treatment of patients and will be equally effective in the prevention of death from cancer.

Introduction

On March 8–9, 2012, the National Cancer Institute convened a meeting to assess the problem of cancer overdiagnosis, which occurs when tumours that would

For some cancers, incidence of disease dropped after screening was initiated (eg, cervical and colon cancer), but it increased for others (eg, breast and prostate cancer).[1] In breast and prostate cancer, for example,

When epidemiologists in 2014 introduced the term *"indolent lesion of epithelial origin, or ILDE,"* they argued explicitly that *"changing the terminology for some of the lesions currently referred to as cancer will allow physicians to shift medico-legal notions."* In other words, diagnoses are sacrificed for the sake of impunity of physicians.

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The new term was proposed *"for those lesions (currently labelled as cancers) and their precursors that are unlikely to cause harm if they are left untreated."* Specific diagnoses were no longer sought; all that mattered was the most likely outcome.

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Addressing overdiagnosis and overtreatment in cancer

Mass screening for solid cancers or precancerous lesions is based on the belief that if cancers can… early—ie, before present… clinical symptoms—therap… likely to be successful. Unf… screening can also some…

the traditional gold standard of expert opinion did not adapt, becoming progressively distanced from its effect on patient populations. Experts in pathology promoted their ability to interpret cellular minutia, leaving it to non-pathologists such as Esserman and colleagues to notice the harm that these interpretations were causing to the pathologists' patients.

links tissue-derived cancer risk to ever evolving therapeutic options could require use of complex and expensive methods not previously applied to the establishment of the risk associated with focal or low-grade morphological aberrations. Esserman and colleagues are optimistic that some challenges to assigning risk will be overcome with scientific advances, but these advances … to achieve. Also, …main aware of the …g underdiagnosis … overdiagnosis. …anges such as

… a workable pathway to diagnostic reform.

Elliot Foucar, 2014

www.thelancet.com/oncology Vol 15 July 2014

Nonetheless, some pathologists, such as Elliot Foucar of Albuquerque, praised that sacrifice of the core of pathology as *"a workable pathway to diagnostic reform.*

The disregard for the specific recognition and designation of biologic entities is become highly prevalent among pathologists.

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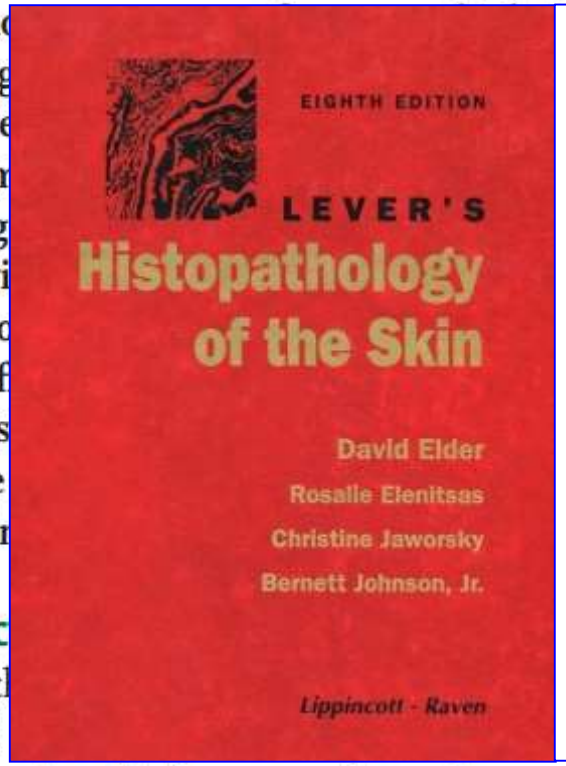

Diagnosis is a clinical tool that assists in the process of categorizing patients into disease groups, within which patients tend to share a common outcome and a common set of responses to therapy. … The most accurate diagnosis is the one that most closely correlates with clinical outcome.

David Elder, 1997

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For example, David Elder, in the introduction to Lever's "Histopathology of the Skin" in 1997, defined diagnosis as follows: *"Diagnosis is a clinical tool that assists in the process of categorizing patients into disease groups, within which patients tend to share a common outcome and a common set of responses to therapy. … The most accurate diagnosis is the one that most closely correlates with clinical outcome."* In that definition, diseases are not thought of as biologic entities but as vague categories defined by outcome or, as Darwin put it in 1859, as "*artificial combinations made for convenience.*"

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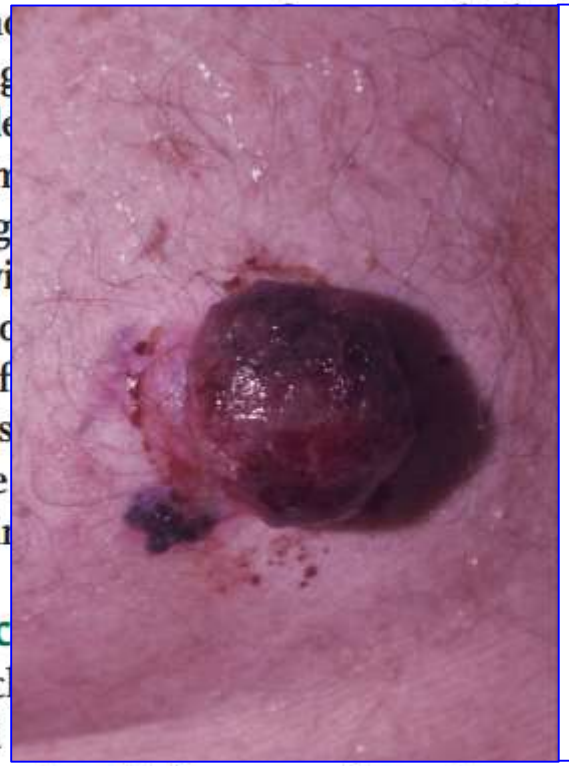

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On March… …after …ncer), convened … …ostate overdiagnosis, which occurs when tumours that would … cancer).[1] In breast and prostate cancer, for example,

By contrast, “the most accurate diagnosis” may be defined, and defined better, as the one that accurately reflects the biologic entity, irrespective of outcome. A thick melanoma that fulfills all clinical and histopathologic criteria for diagnosis is a melanoma, whether or not the patient succumbs to it,

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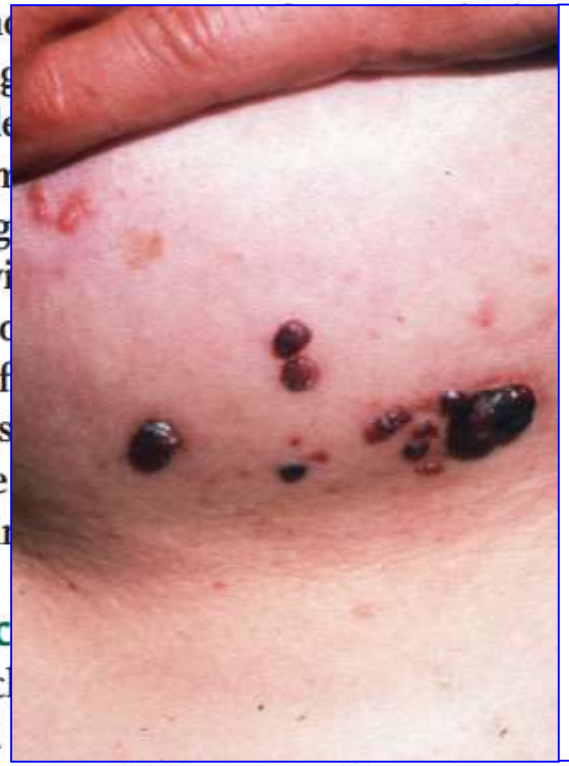

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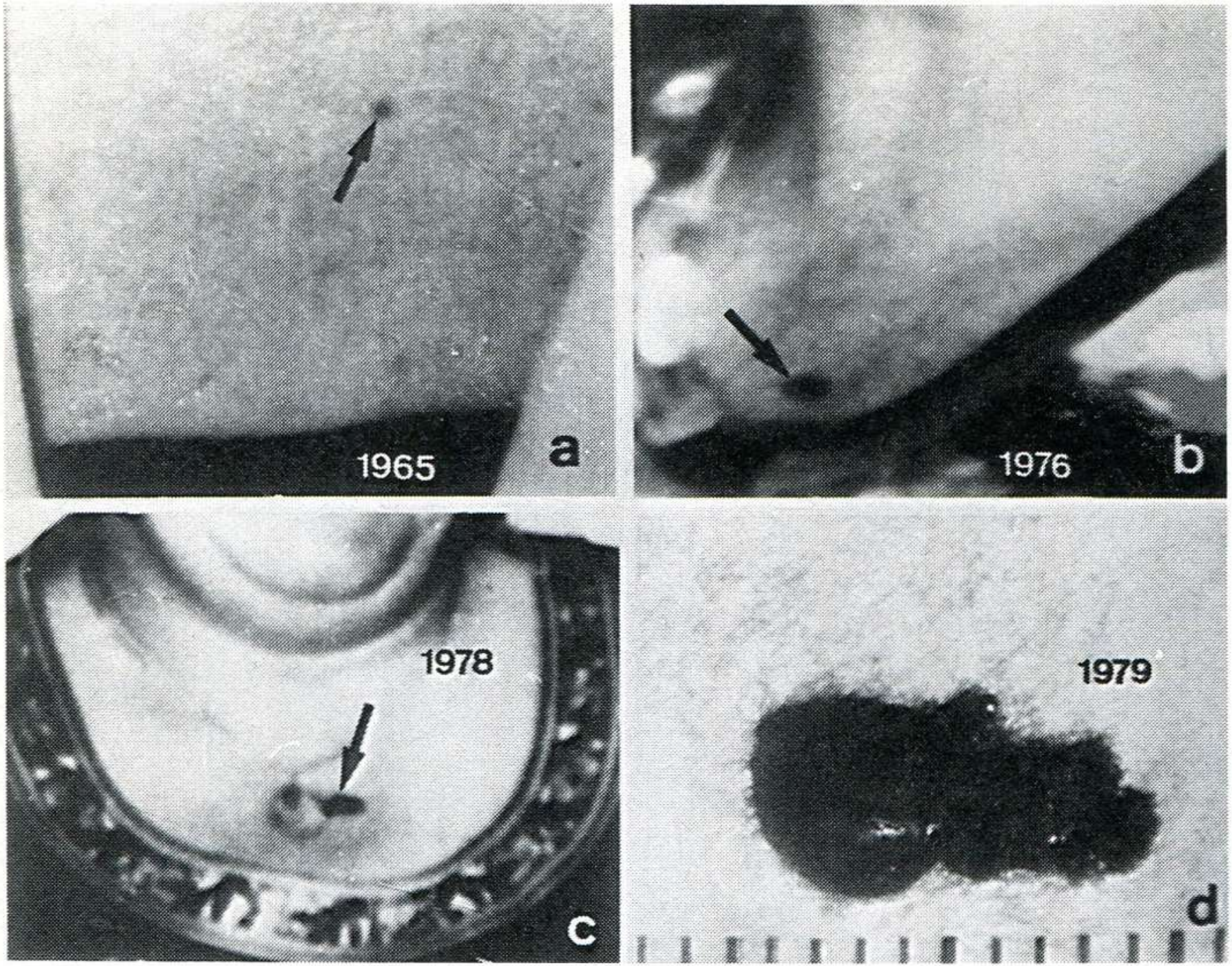
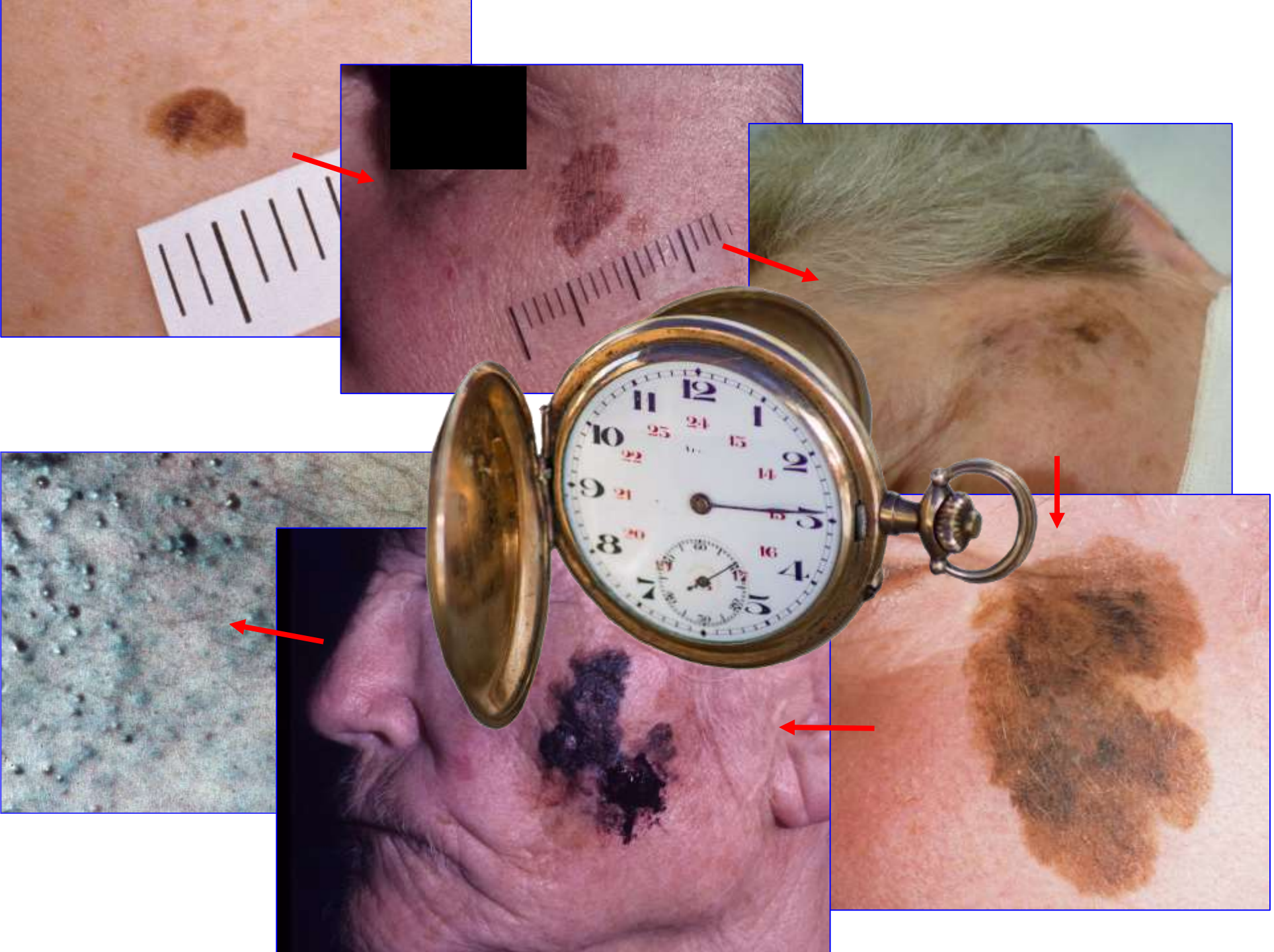
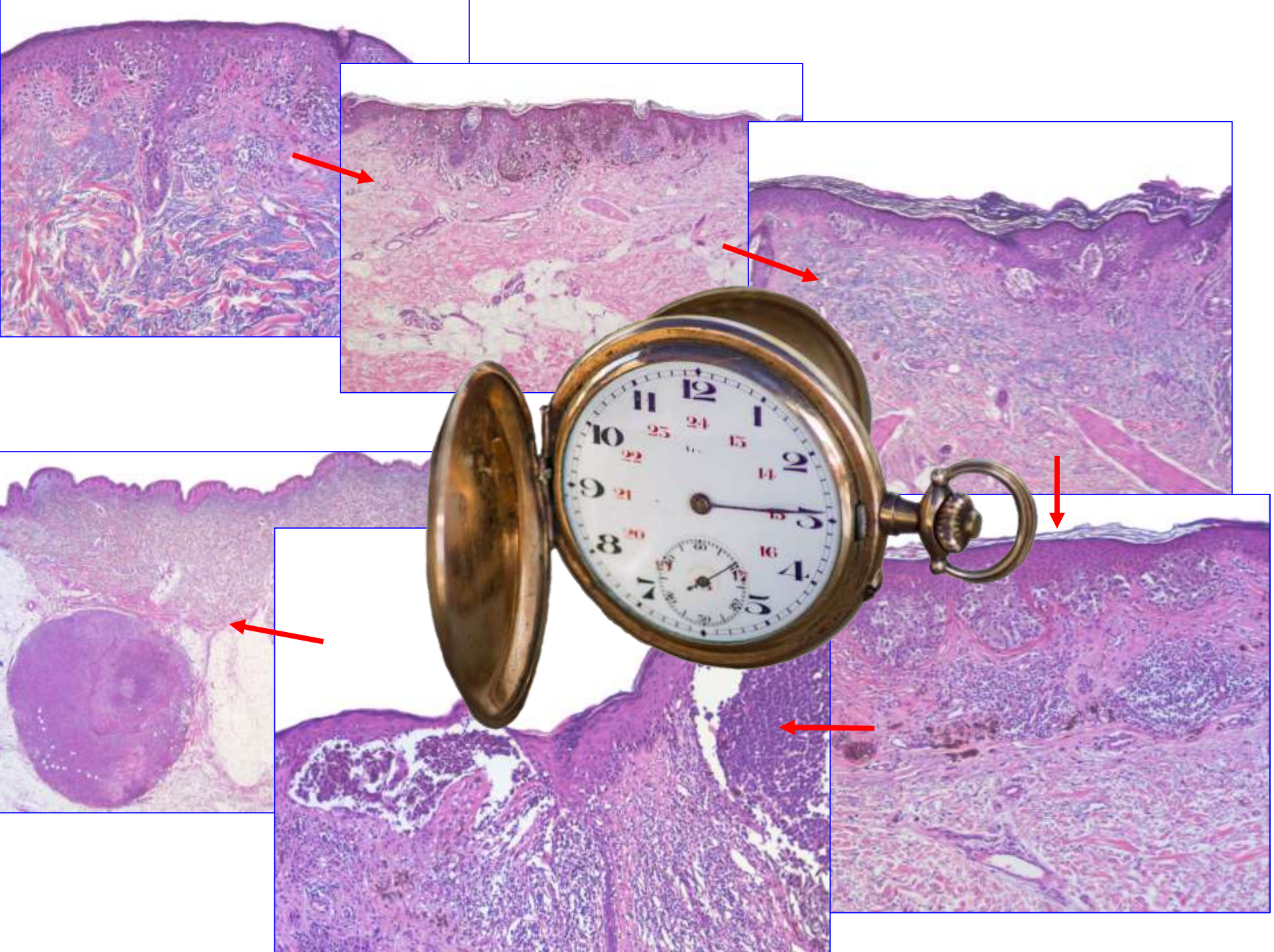
and a metastatic melanoma is a metastatic melanoma, even if all metatases should regress spontaneously, as they sometimes do.



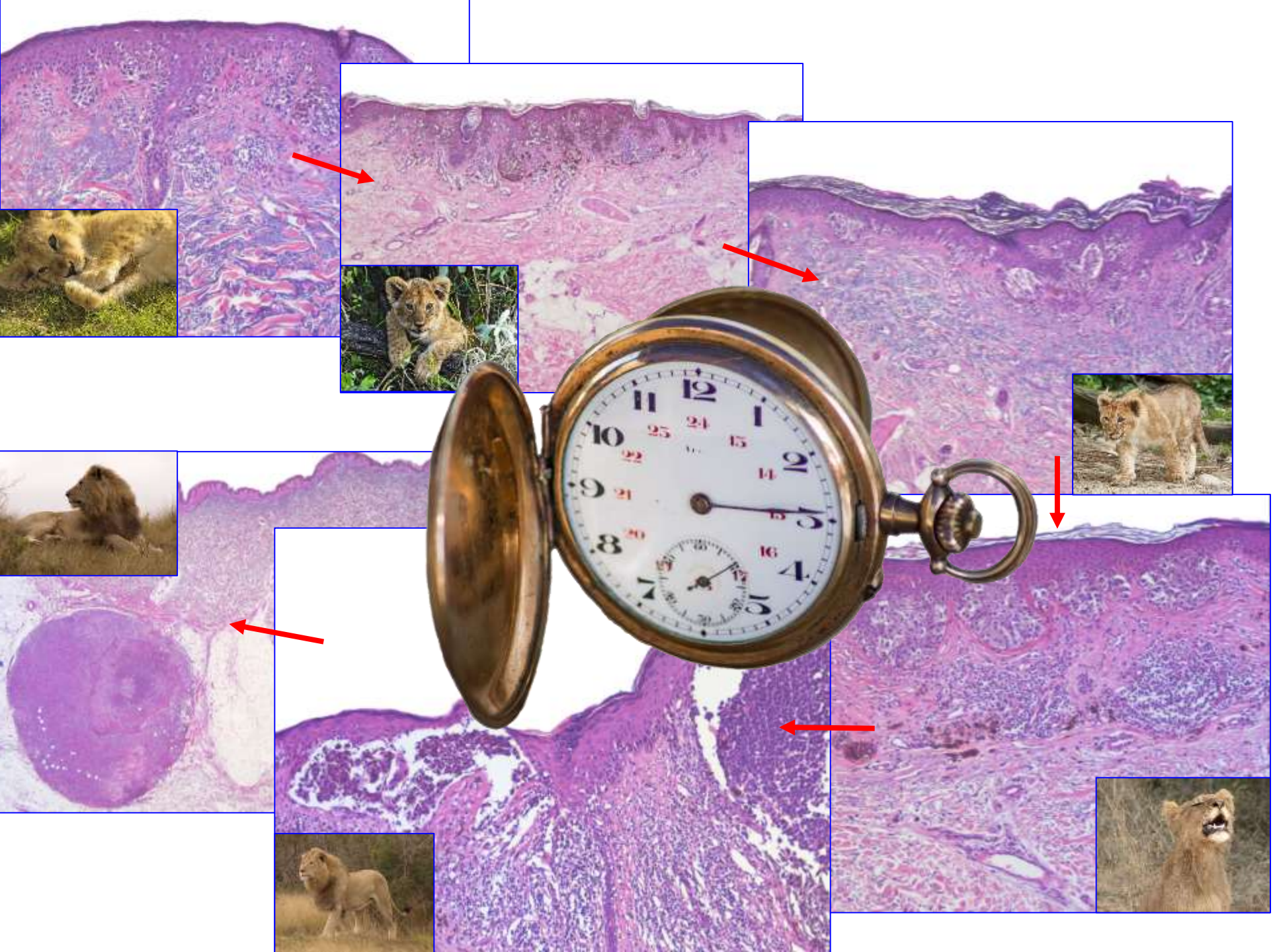
The development of melanoma is a continuous process that can often been documented over years.



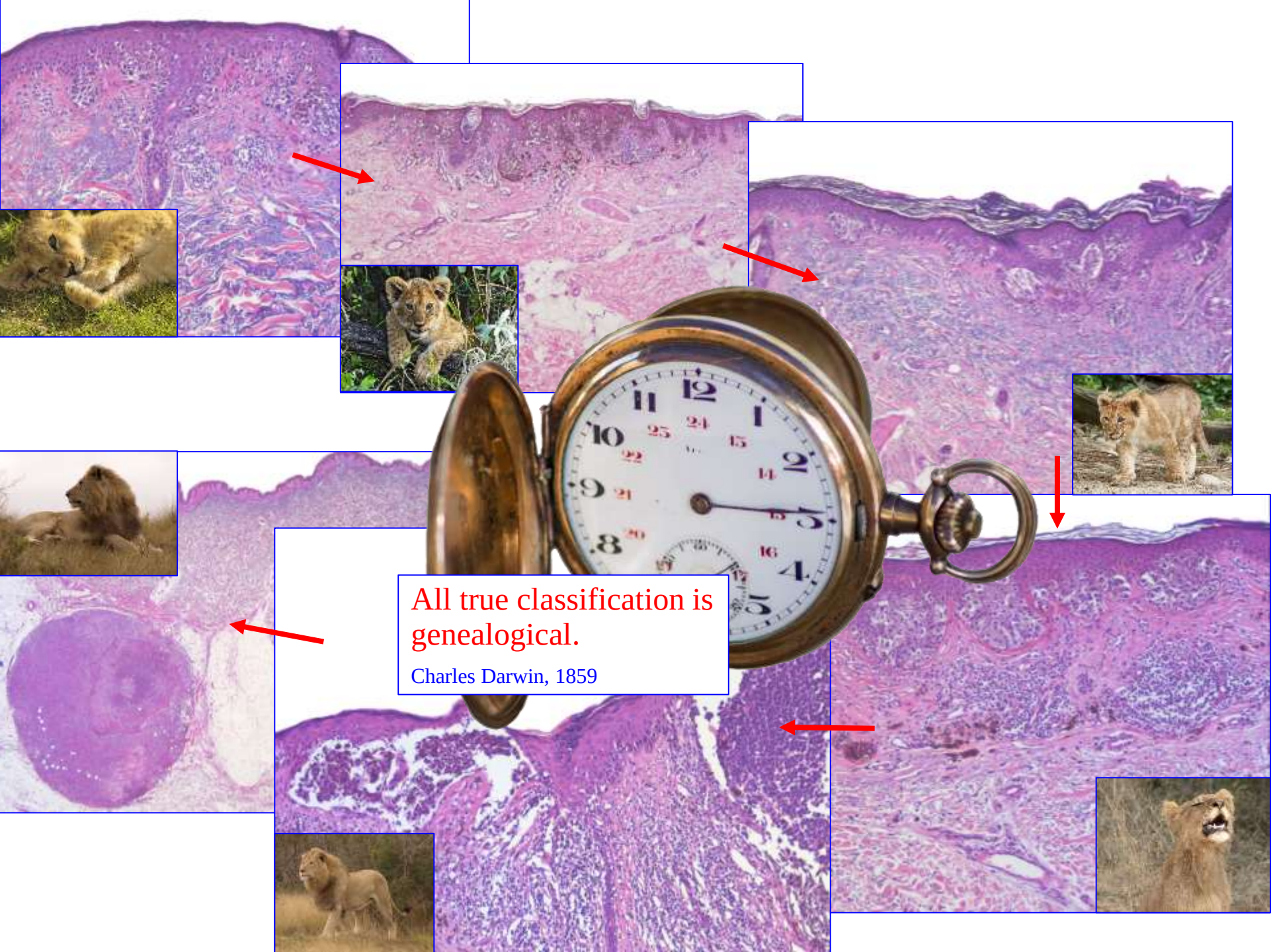
Clinical criteria of maligancy, such as asymmetry, uneven pigmentation, and irregular outline, are usually detectbable at an in-situ stage.



This is even more true for histopathologic criteria, such as melanocytes in the upper reaches of the epidermis and irregular configuration and distribution of nests. But even when dealing clearly with manifestations of the same biologic process, early stages are being separated from later ones, in melanomas just as in carcinomas, based on the notion that they are “biologically benign.”



By the same token, one could argue that a lion puppy is no lion because it is not yet dangerous. However, experience tells that, if allowed to live, it grows and changes its metabolism, appearance, and behavior. Constant change at all hierarchical levels is an attribute of each and every biologic entity. This also applies to melanoma, which, in its lifetime, undergoes not only quantitative but also major qualitative changes. Those changes are implied in the concept of species.



As Darwin noted, *"all true classification is genealogical."* If advanced melanomas develop nearly invariably from in-situ melanomas and, as a rule, sport remnants of in-situ melanoma at their edges, the genealogical evidence demands classification of those lesions as examples of a single species at different stages of development. Because behaviour depends on the stage of evolution, a specific diagnosis does not suffice but should be supplemented by a gauge of prognosis. It makes a big difference whether one is dealing with a melanoma in situ, a nodule of melanoma, or a metastasis. However, prognosis cannot supplant or replace diagnosis.

CME ARTICLE

Next-Generation Sequencing Reveals Pathway Activations and New Routes to Targeted Therapies in Cutaneous Metastatic Melanoma

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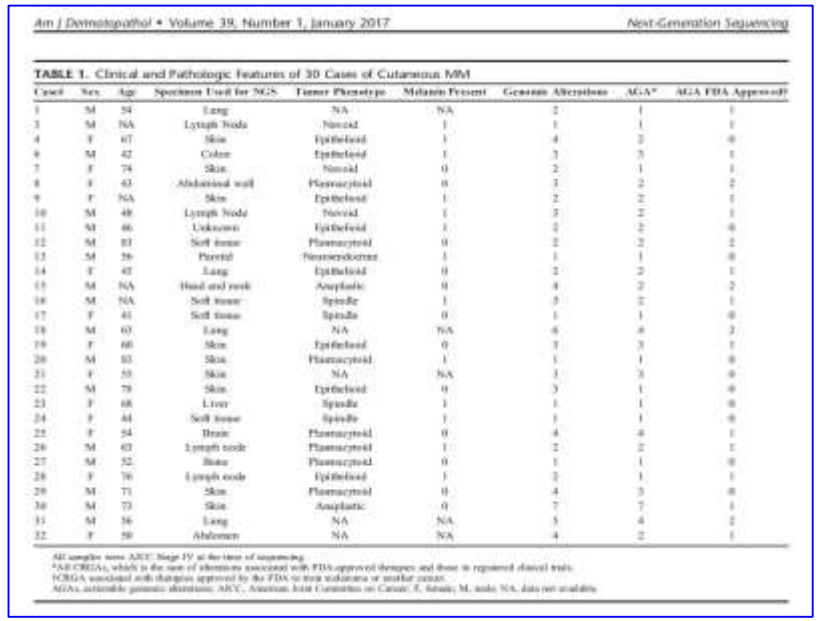

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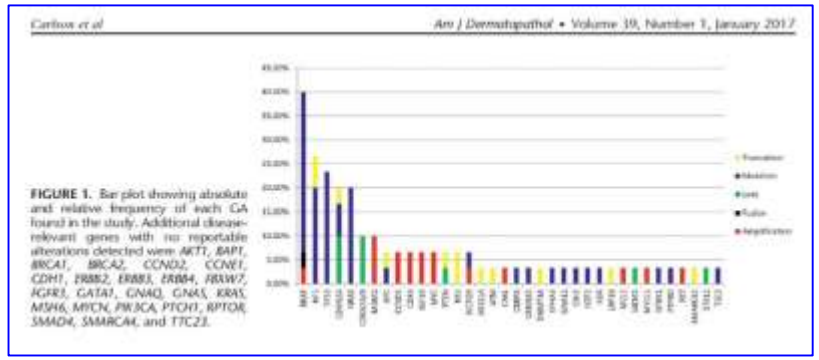
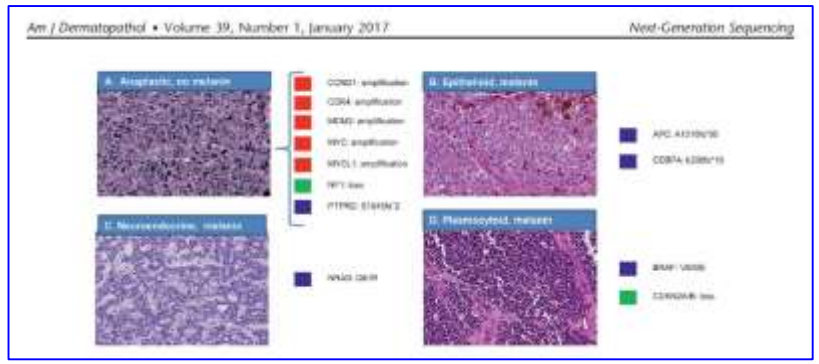


FIGURE 1. Bar plot showing absolute and relative frequency of each GA found in the study. Additional disease-relevant genes with no reportable alterations detected were: *AKT1, BAP1, BRCA1, BRCA2, CCND2, CCNE1, CDH1, ERBB2, ERBB3, ERBB4, HRAS7, IGFR1, GATA1, GNAQ, GNAS, KRAS, MSH6, MYCN, PIK3CA, PTCH1, RPTOR, SMAD4, SMARCA4,* and *TTC23.*



The same applies to molecular alterations that allow for specific forms of treatment, such as BRAF or KIT mutations. Although important for the management of individual patients, those findings are of secondary importance and unrelated to the diagnostic process.

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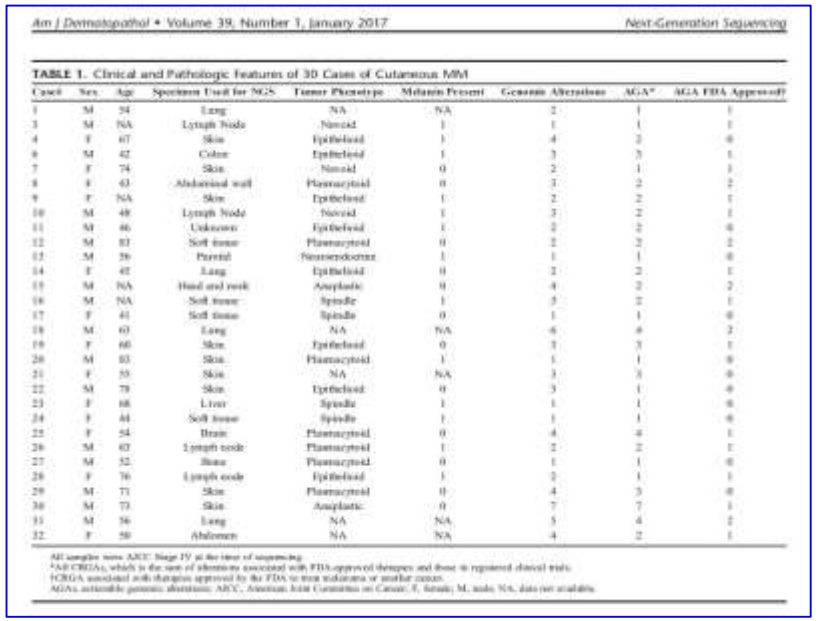

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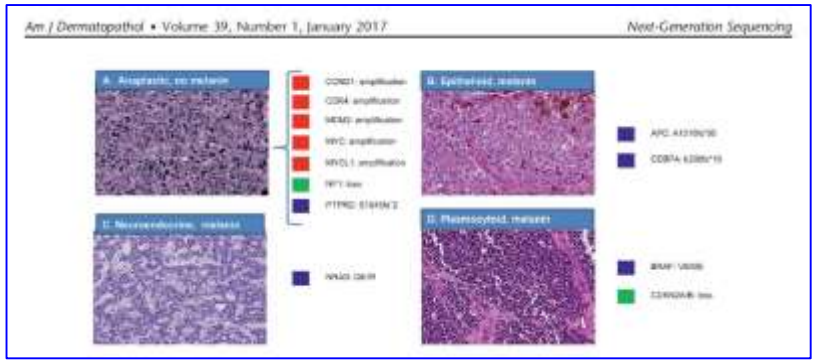

As Andrea Cesalpino noted in 1593 in regard to plants, the latter focusses on *"similarities and dissimilarities of form, in which the essence … consists, but not of things which are merely accidents, [such as] medicinal virtues and other useful qualities."* Findings allowing for an estimation of prognosis or a special type of treatment are "useful qualities," and one must be versatile with them,

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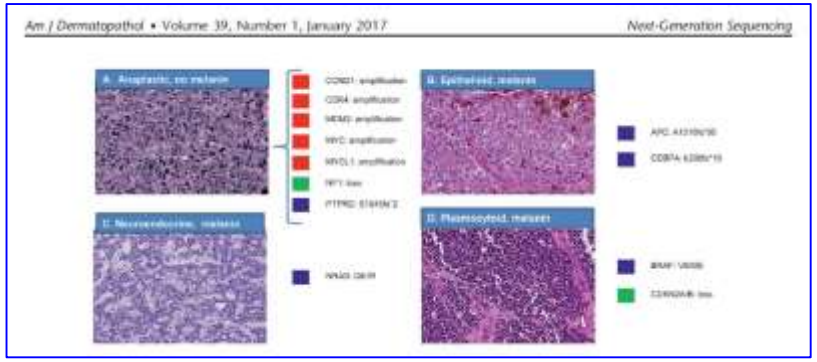

just as a botanist should not only know how to recognize species of plants but also how to treat them. The primary task, however, is recognition of the biologic entity, without which any statement concerning prognosis or treatment remains vague and precarious.

Modern Pathology (2006) 19, S21–S33

www.modernpathology.org

The Spitzoid lesion: rethinking Spitz tumors, atypical variants, 'Spitzoid melanoma' and risk assessment

Raymond L Barnhill

Departments of Dermatology and Pathology, University of Miami Miller School of Medicine, Miami, FL, USA

Although much remains to be learned about Spitzoid lesions, there is increasing evidence that these tumors may be a type of melanocytic neoplasm distinct from conventional melanocytic nevi and malignant melanoma. In the current communication, the author has attempted to describe accurately the state-of-the-art surrounding these lesions, their nomenclature, and assessment of risk. Acknowledging the peculiar nature of Spitzoid lesions, the author prefers the term Spitz tumor rather than 'Spitz nevus' (except perhaps for the most typical lesions) and argues against using the term 'Spitzoid melanoma' until more information is available to justify such a term. The author also believes that patients are best served by the comprehensive evaluation of Spitzoid lesions and their classification into three categories: (1) Spitz tumor without significant abnormality, (2) Spitz tumor with one or more atypical features (atypical Spitz tumor), including those judged to have indeterminate biological potential, and (3) malignant melanoma, rather than the two categories of 'Spitz nevus' and melanoma. Only rigorous characterization of sufficient numbers of Spitzoid lesions and long-term follow-up of patients will provide truly objective information for the formulation of optimal guidelines for the management of patients with these lesions.
Modern Pathology (2006) **19**, S21–S33. doi:10.1038/modpathol.3800519

Keywords: Spitz nevus, Spitz tumor, melanoma

Nonetheless, it has become commonplace to utter statements about prognosis in the absence of a diagnosis. For example, in regard to "spitzoid lesions," some authors have suggested to refrain from a diagnosis and to engage in *"risk assessment"*

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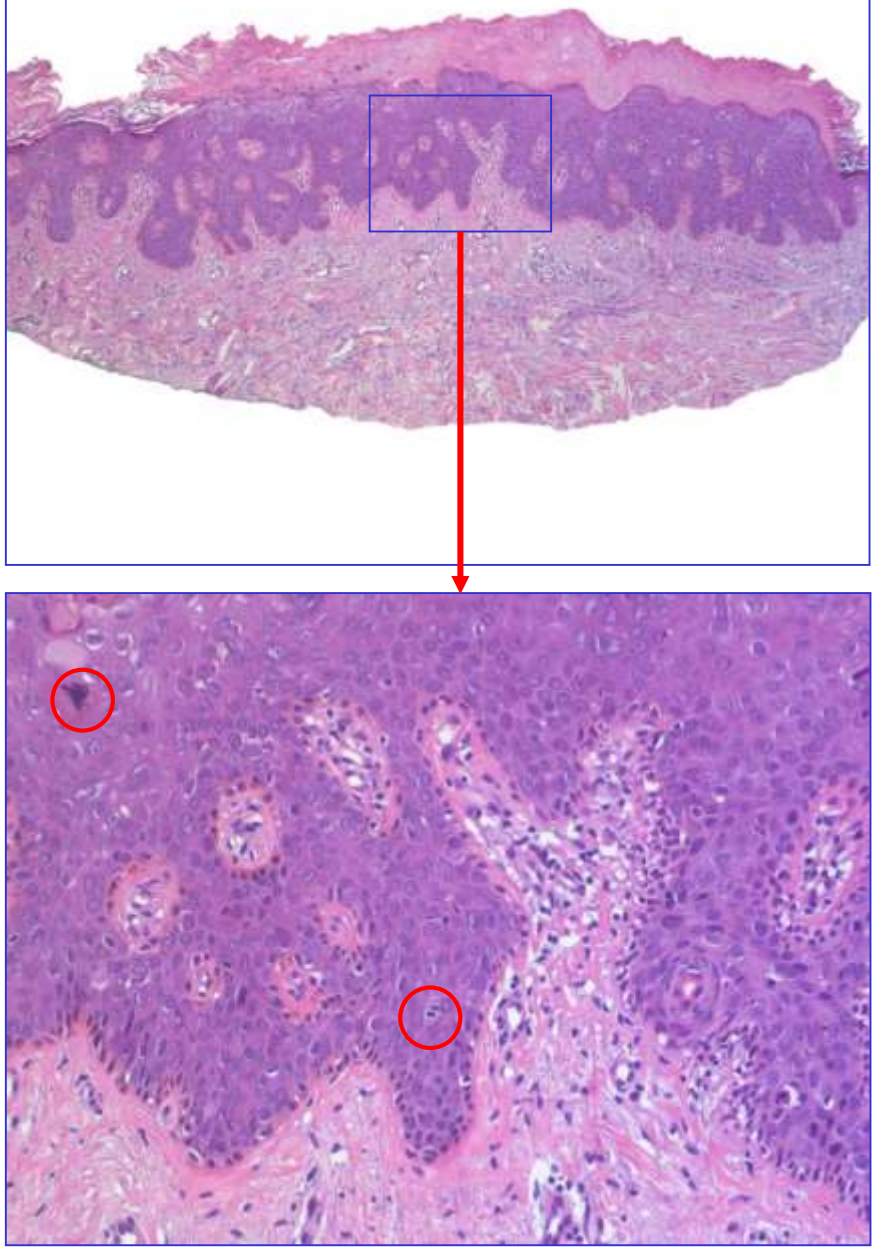
Table 6 Assessment of Spitz tumors in children and adolescents for risk for metastasis[30]

Parameter	*Score*[a]
Age (years)	
0–10	0
11–17	1
Diameter (mm)	
0–10	0
>10	1
Involvement of subcutaneous fat	
Absent	0
Present	2
Ulceration	
Absent	0
Present	2
Mitotic activity (mm²)	
0–5	0
6–8	2
>9	5

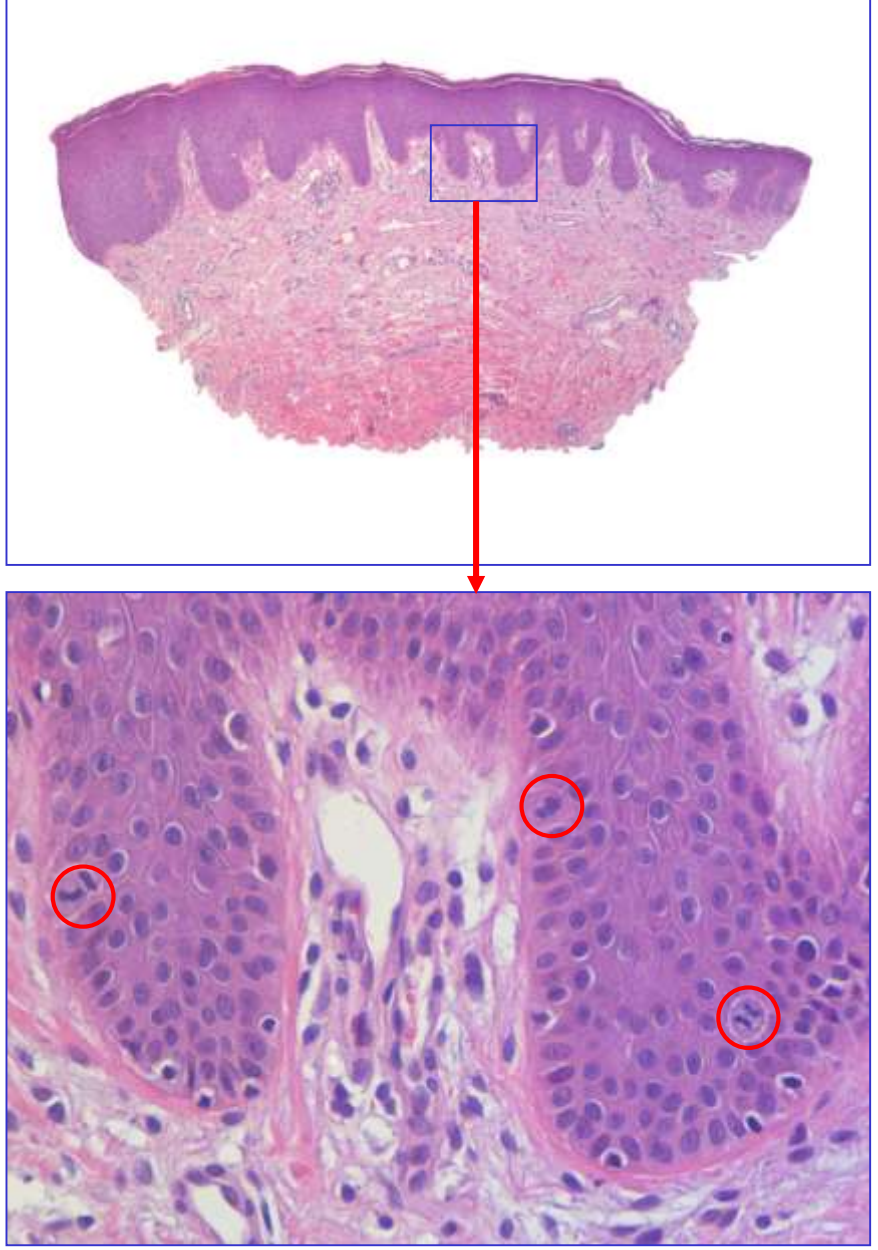
[a]Total score indicates increasing risk for metastasis.

by adding up prognostic factors such as age, diameter, and mitotic activity. This is the same

Morbus Bowen



Psoriasis



as if not distinguishing between Bowen's disease and psoriasis but trying to predict outcome by the degree of epithelial hyperplasia and the number of mitotic figures,

or if not distinguishing between sheep and dogs but trying to predict behavior based on the color of their fur

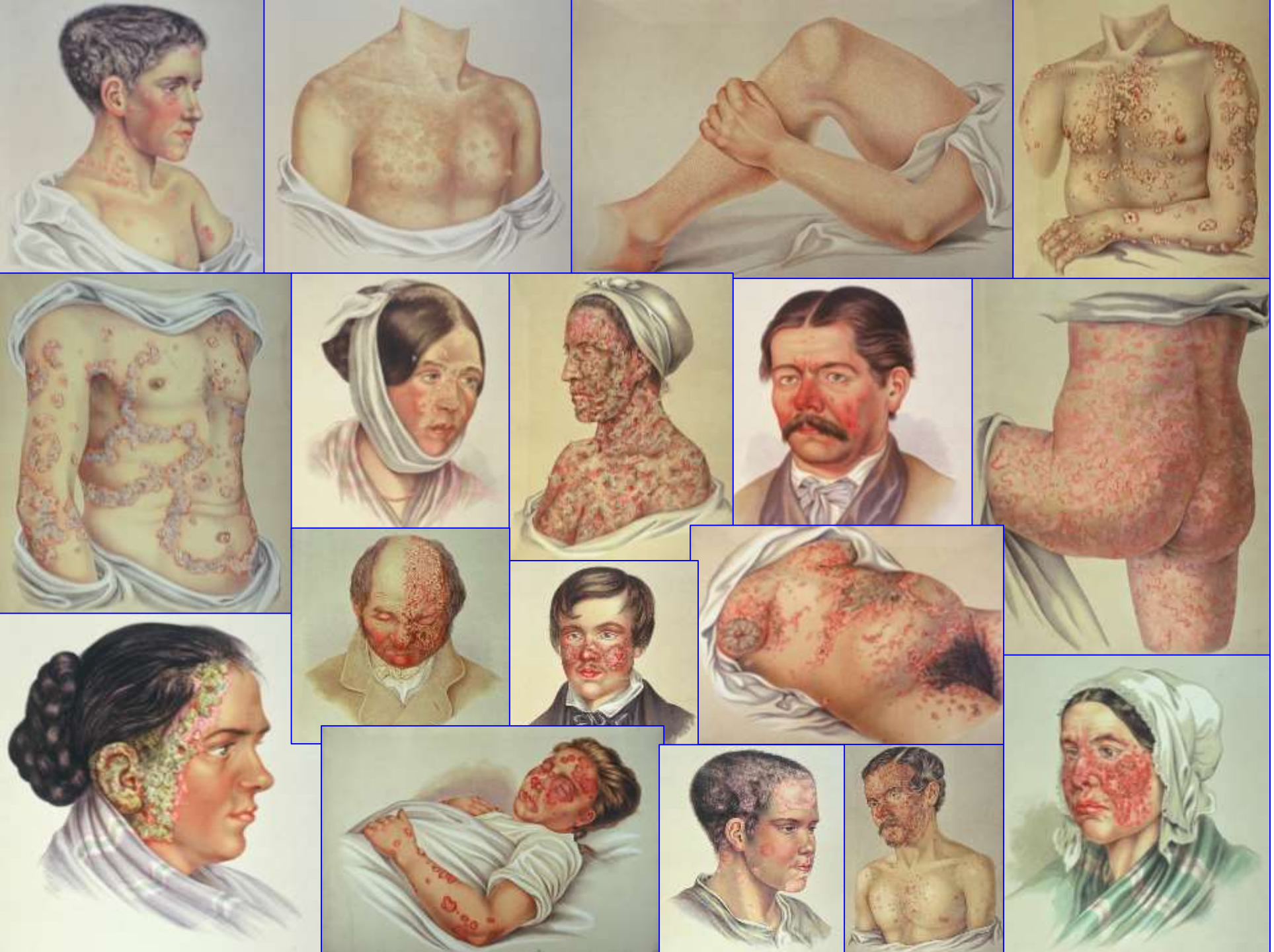
and the size of their teeth. Obviously, before any statement about potential behavior can be made, a diagnosis is essential. Recognition of biologic entities may not be easy, but, in general, it is possible on the basis of a constellation of criteria, and the more we can assess, not only fur and teeth,

but also nose, eyes, ears,

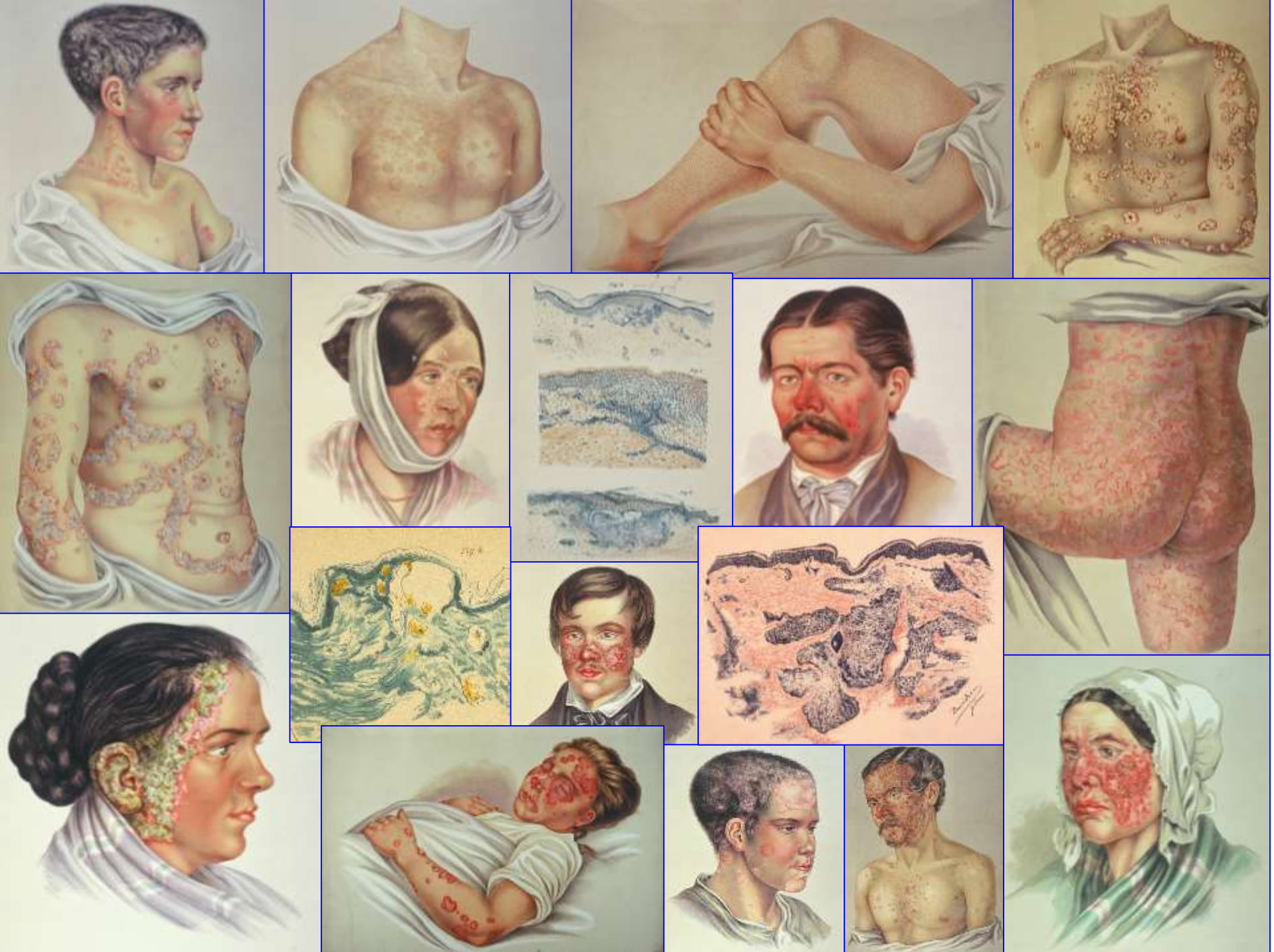
and maybe legs, the easier it gets. Once a diagnosis has been made, certain assumptions concerning behavior are justified. For example, sheep tend to grass. This does not imply that behavior can be calculated;

surprises cannot be excluded. But if we base our acumen on aspects of behavior,

meaningful statements are impossible.

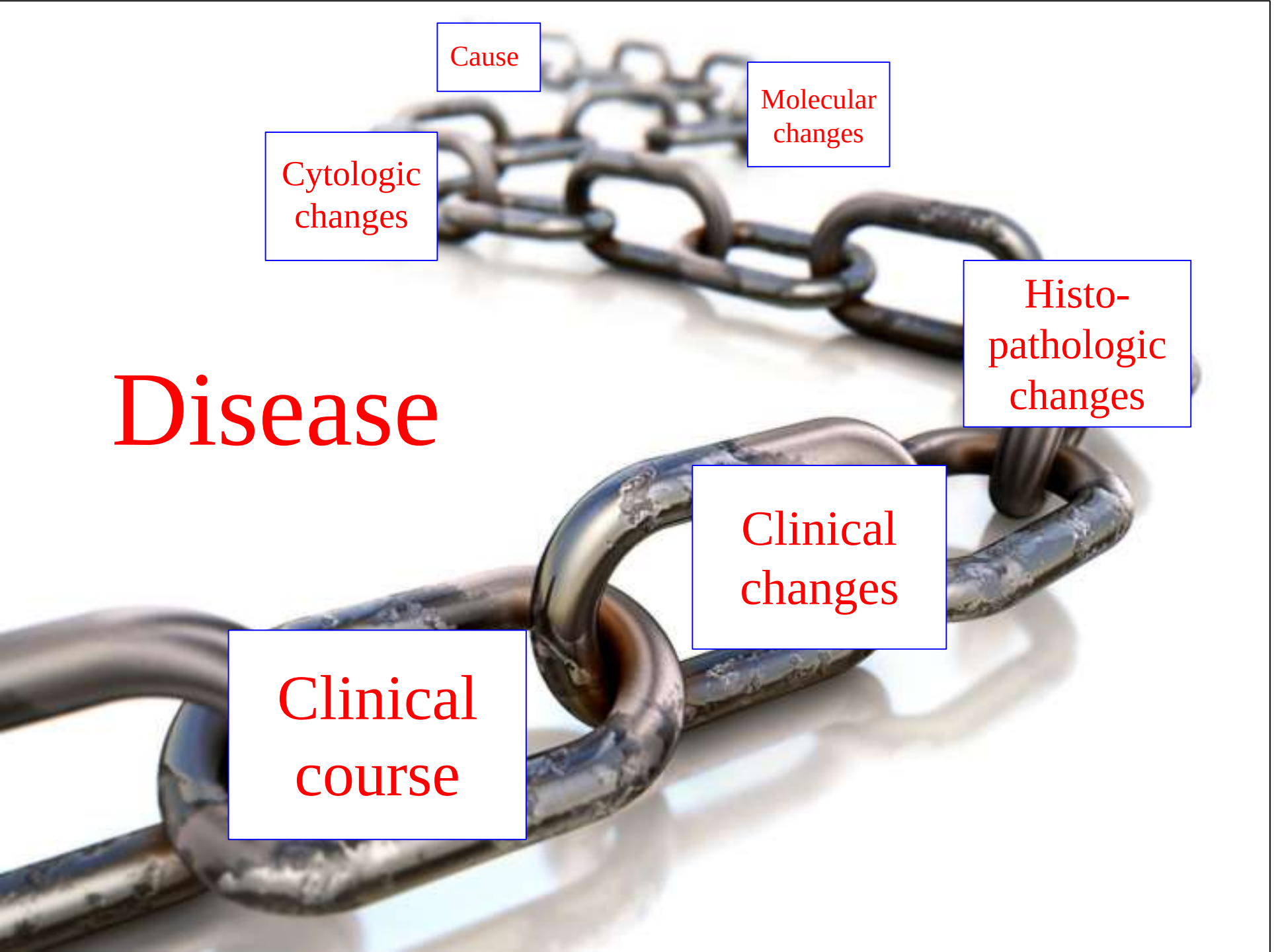


Fortunately, diseases offer just as many criteria for diagnosis as animals and plants. This is especially true for skin diseases because of the diversity of cutaneous changes, the opportunity to perform pinpoint biopsies under direct visual control at carefully selected sites,



and the abundance of histopathologic criteria for differential diagnosis. There are also many other findings that can be utilized,

ranging from molecular changes and serologic parameters to associated symptoms and clinical course. This is what distinguished a disease from a patterns:

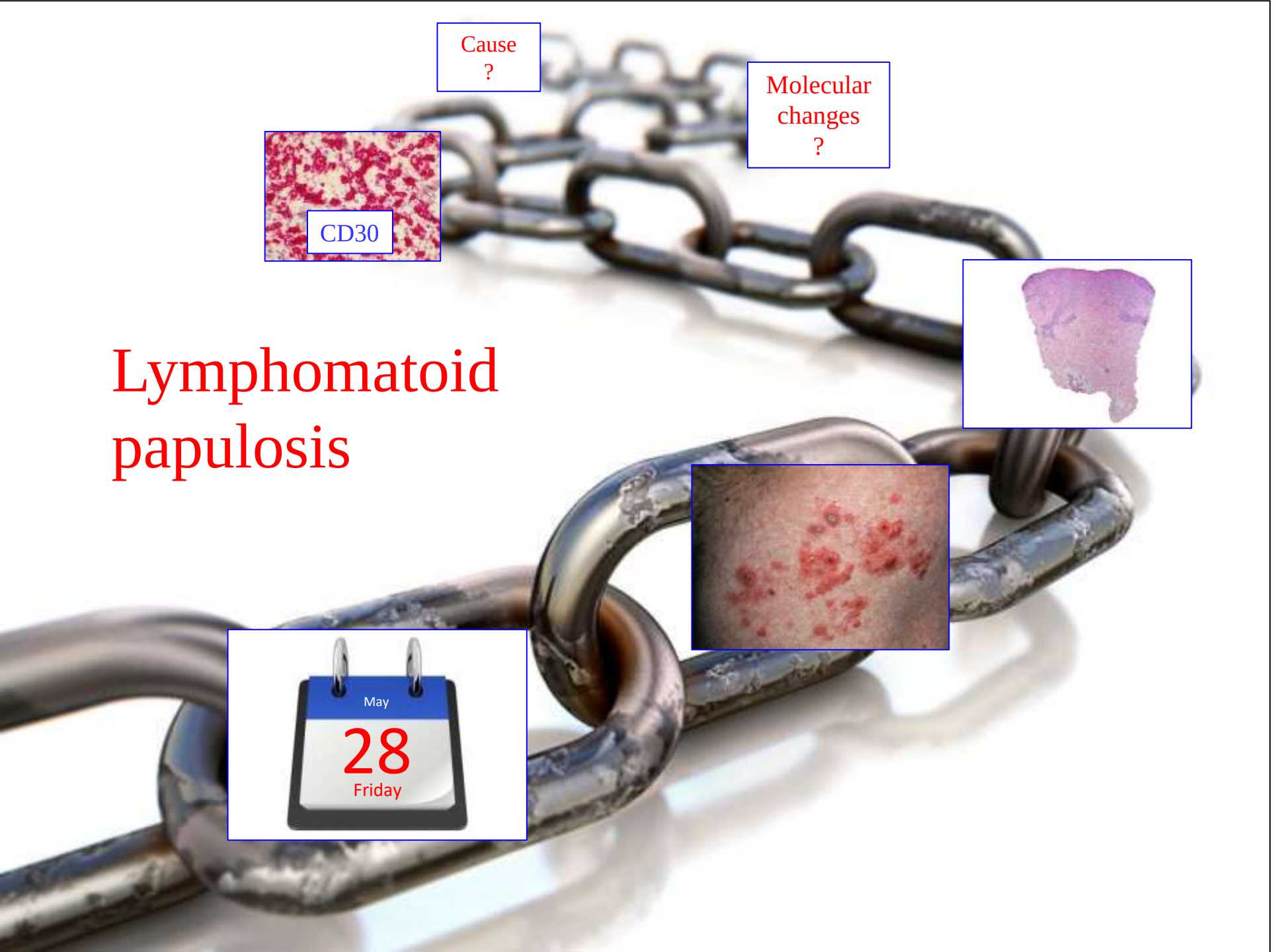


a disease is a process, a chain of events at many different levels, and although the skin can react in only a limited number of ways at each level, the combination of patterns at different levels explains the enormous variety and distinctiveness of diseases that allow so many species to be recognized.

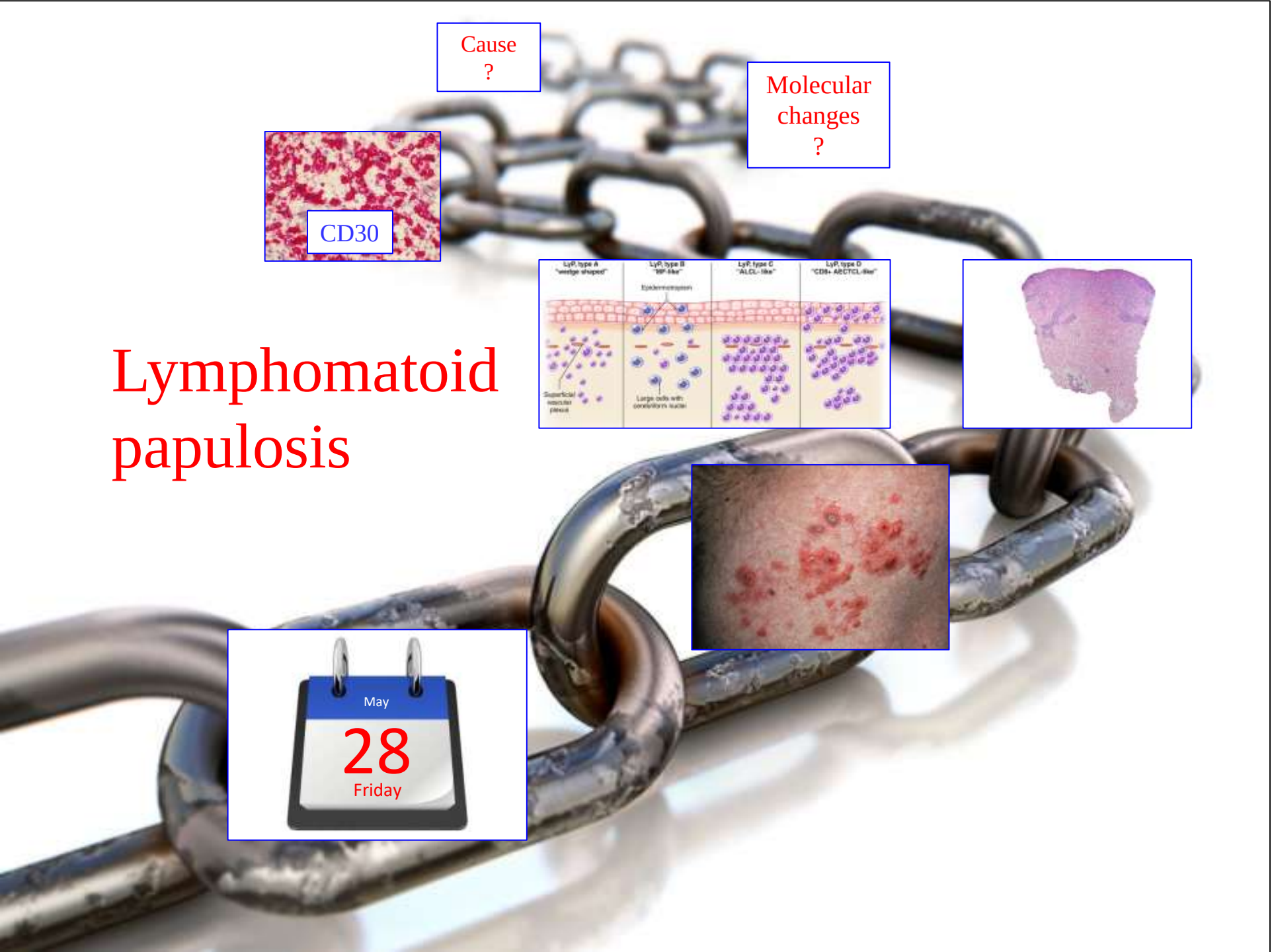
If not all links in the chain of events are known, this does not diminuish the specificity of the disease.

Herpes labialis

In some diseases, essential factors are known at basically every level, and sometimes findings at at a single level are enough for specific recognition, such as demonstration of the virus, or a specific immune response on a molecular level, or cytopathologic and histopathologic changes, or the clinical presentation, or the characteristic repetitive course of infections by herpes simplex virus.

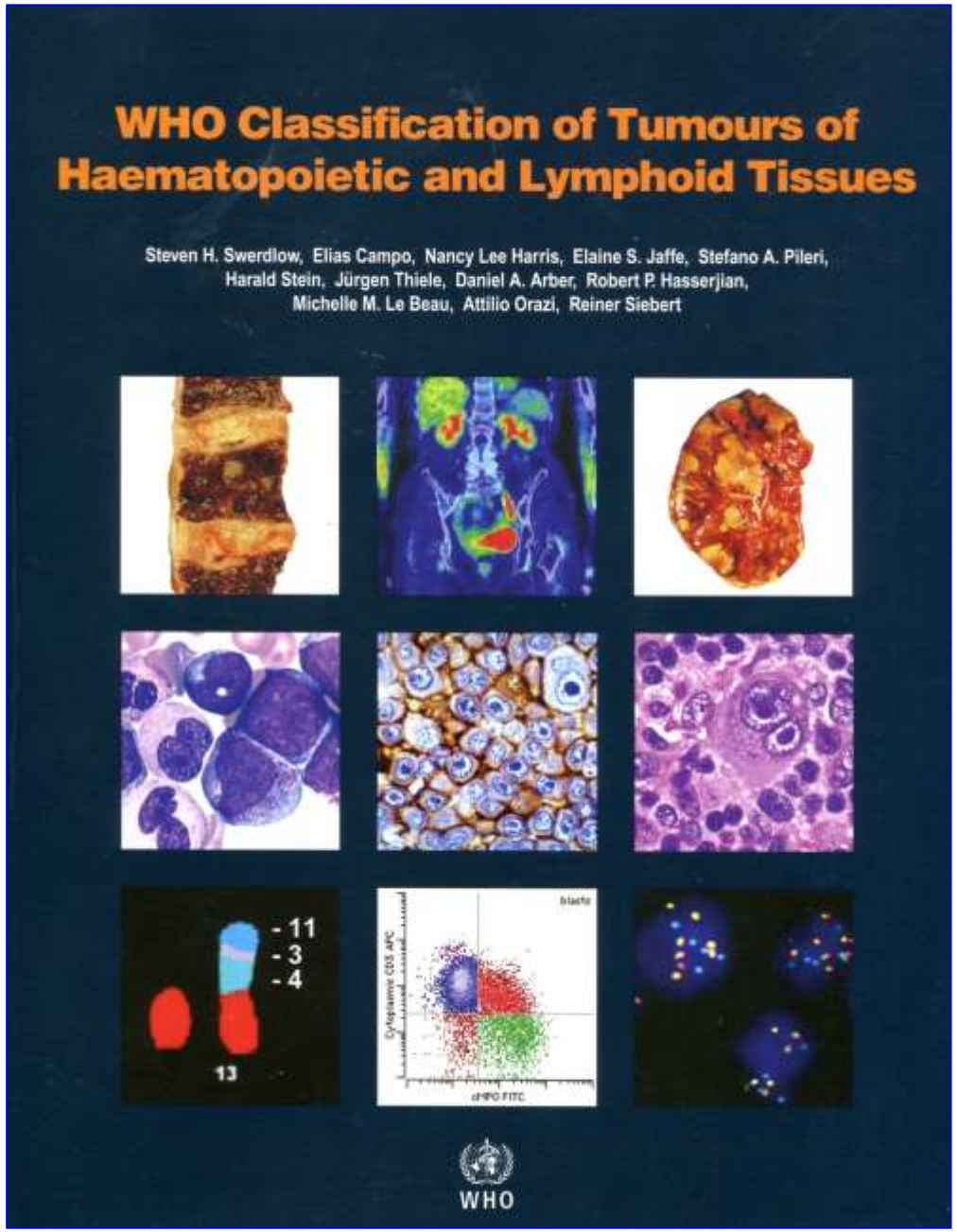


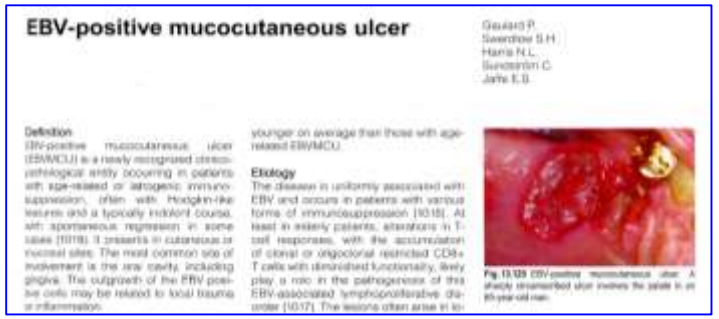
In other diseases, all that is known must be integrated for a specific diagnosis to be reached, e.g., cytologic and histopathologic changes, clinical presentation, and the characteristic course in lymphomatoid papulosis. Specificity requires a constellation of correlated criteria across several levels. Correlated criteria at only one level are not enough,



as demonstrated by the different histopathologic types of lymphomatoid papulosis that may occur in combination, and without any impact on the biologic course, in the same patient.
In recent years, chances for correlation across several hierarchical leves have been enhanced significantly by new techniques.

Immunohistochemical and molecular findings have contributed to better characterization of known, and definition and recognition of previously unknown, diseases.





EBV-positive mucocutaneous ulcer

Gaulard P.
Swerdlow S.H.
Harris N.L.
Sundström C.
Jaffe E.S.

Definition

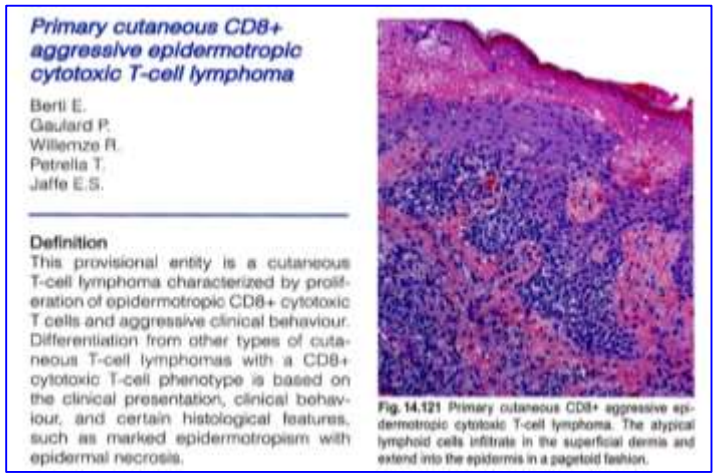
EBV-positive mucocutaneous ulcer (EBVMCU) is a newly recognized clinicopathological entity occurring in patients with age-related or iatrogenic immunosuppression, often with Hodgkin-like features and a typically indolent course, with spontaneous regression in some cases [1078]. It presents in cutaneous or mucosal sites. The most common site of involvement is the oral cavity, including gingiva. The outgrowth of the EBV-positive cells may be related to local trauma or inflammation.

younger on average than those with age-related EBVMCU.

Etiology

The disease is uniformly associated with EBV and occurs in patients with various forms of immunosuppression [1018]. At least in elderly patients, alterations in T-cell responses, with the accumulation of clonal or oligoclonal restricted CD8+ T cells with diminished functionality, likely play a role in the pathogenesis of this EBV-associated lymphoproliferative disorder [1017]. The lesions often arise in lo-

Fig. 13.125 EBV-positive mucocutaneous ulcer. A sharply circumscribed ulcer involves the palate in an 81-year-old man.



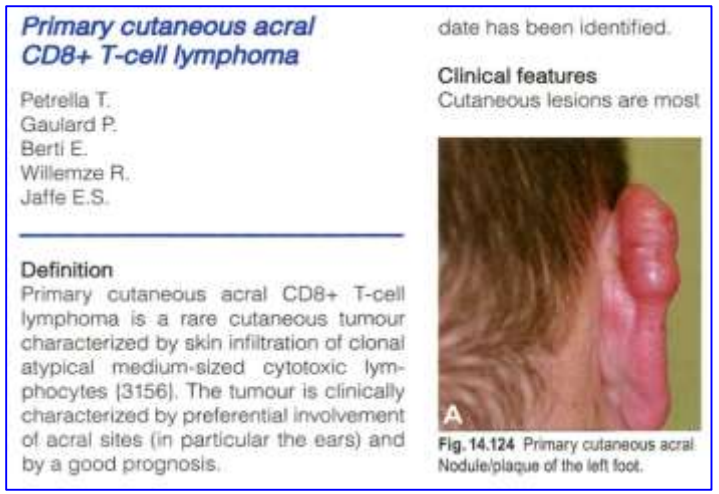
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma

Berti E.
Gaulard P.
Willemze R.
Petrella T.
Jaffe E.S.

Definition

This provisional entity is a cutaneous T-cell lymphoma characterized by proliferation of epidermotropic CD8+ cytotoxic T cells and aggressive clinical behaviour. Differentiation from other types of cutaneous T-cell lymphomas with a CD8+ cytotoxic T-cell phenotype is based on the clinical presentation, clinical behaviour, and certain histological features, such as marked epidermotropism with epidermal necrosis.

Fig. 14.121 Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma. The atypical lymphoid cells infiltrate in the superficial dermis and extend into the epidermis in a pagetoid fashion.



Primary cutaneous acral CD8+ T-cell lymphoma

Petrella T.
Gaulard P.
Berti E.
Willemze R.
Jaffe E.S.

Definition

Primary cutaneous acral CD8+ T-cell lymphoma is a rare cutaneous tumour characterized by skin infiltration of clonal atypical medium-sized cytotoxic lymphocytes [3156]. The tumour is clinically characterized by preferential involvement of acral sites (in particular the ears) and by a good prognosis.

date has been identified.

Clinical features

Cutaneous lesions are most

Fig. 14.124 Primary cutaneous acral Nodule/plaque of the left foot.

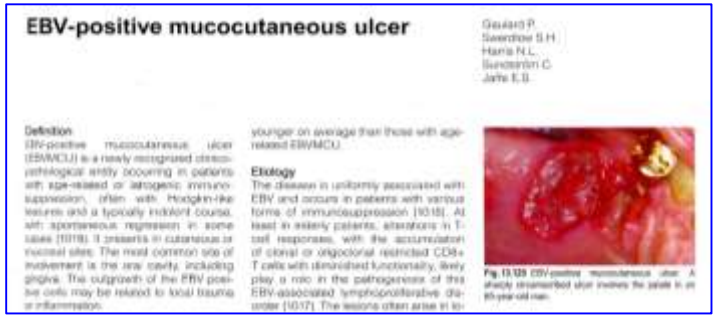
An example is the expanding spectrum of lymphomas that has been enriched gradually by newly recognized entities. In the current “WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues,” the editors followed principles of classification in biology at large, trying to distinguish accidental constellations of findings from what they called *“‘real’ diseases.”*

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Steven H. Swerdlow, Elias Campo, Nancy Lee Harris, Elaine S. Jaffe, Stefano A. Pileri, Harald Stein, Jürgen Thiele, Daniel A. Arber, Robert P. Hasserjian, Michelle M. Le Beau, Attilio Orazi, Reiner Siebert

A classification should contain diseases that are clearly defined, clinically distinctive, , and non-overlapping (i.e. mutually exclusive), and that together constitute all known entities (i.e. are collectively exhaustive) … the underlying causes of these neoplasms are often unknown and may vary. Therefore, the WHO approach to classification incorporates all available information – morphology, immunophenotype, genetic features, and clinical features – to define the diseases. The relative importance of each of these features varies by disease, depending on the current state of knowledge; there is no single gold standard by which all diseases are defined.

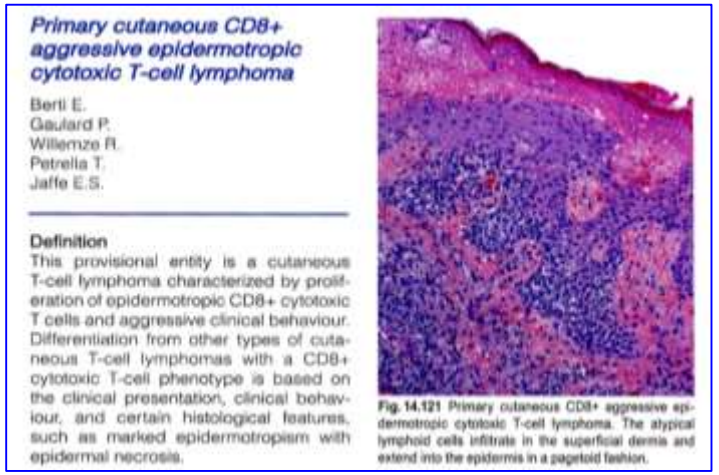
WHO



EBV-positive mucocutaneous ulcer

Definition

Etiology



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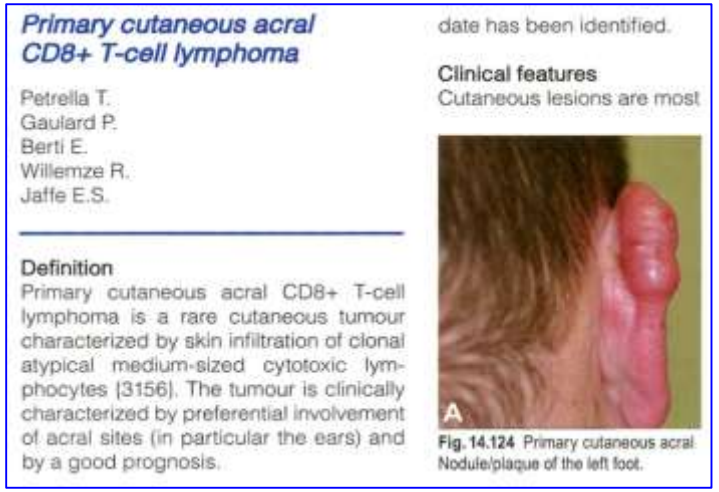

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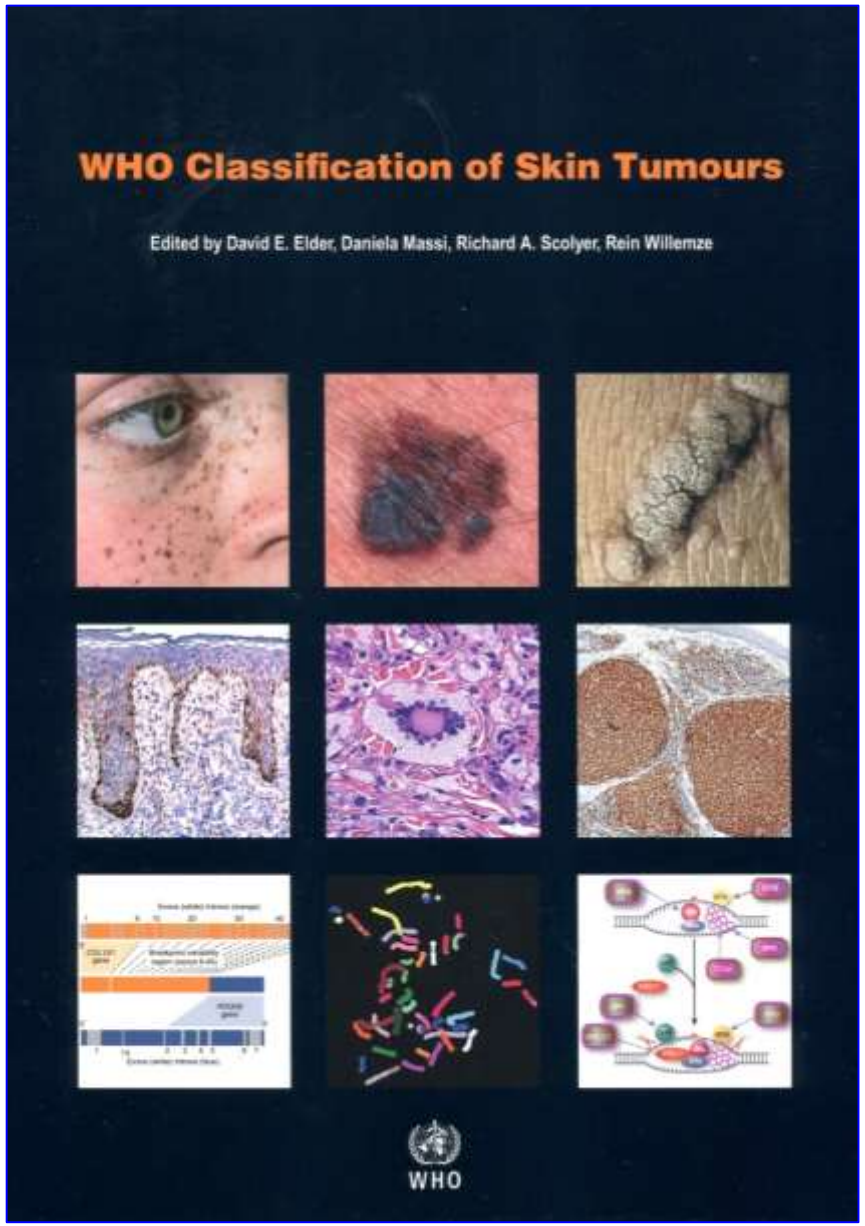
date has been identified.

Clinical features

Cutaneous lesions are most

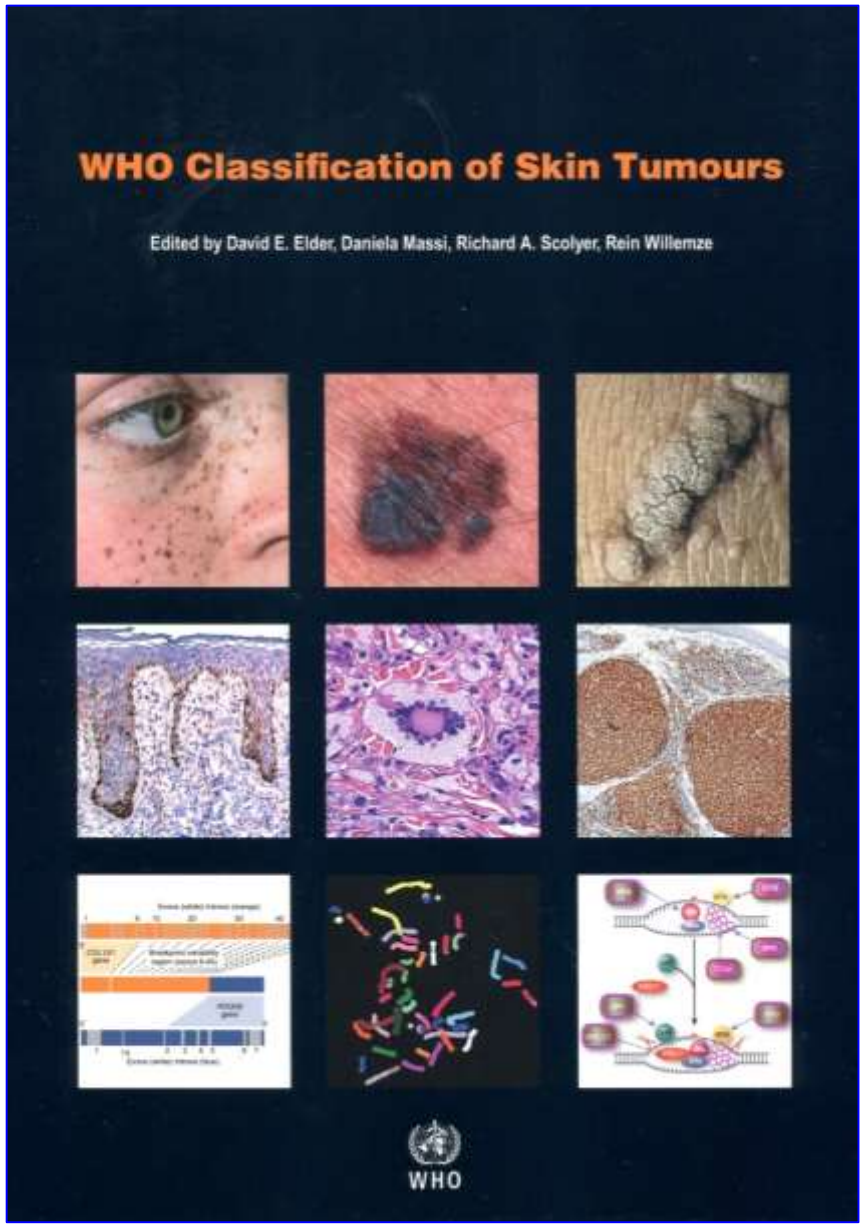
Fig. 14.124 Primary cutaneous acral Nodule/plaque of the left foot.

Because *"the underlying causes of these neoplasms are often unknown and may vary,"* they incorporated *"all available information – morphology, immunophenotype, genetic features, and clinical features – to define the diseases"* and emphasized that *"the relative importance of each of these features varies by disease, depending on the current state of knowledge; there is no single gold standard by which all diseases are defined."* The goal was a classification containing *"diseases that are clearly defined, clinically distinctive, and non-overlapping (i.e. mutually exclusive), and that together constitute all known entities (i.e. are collectively exhaustive)."*



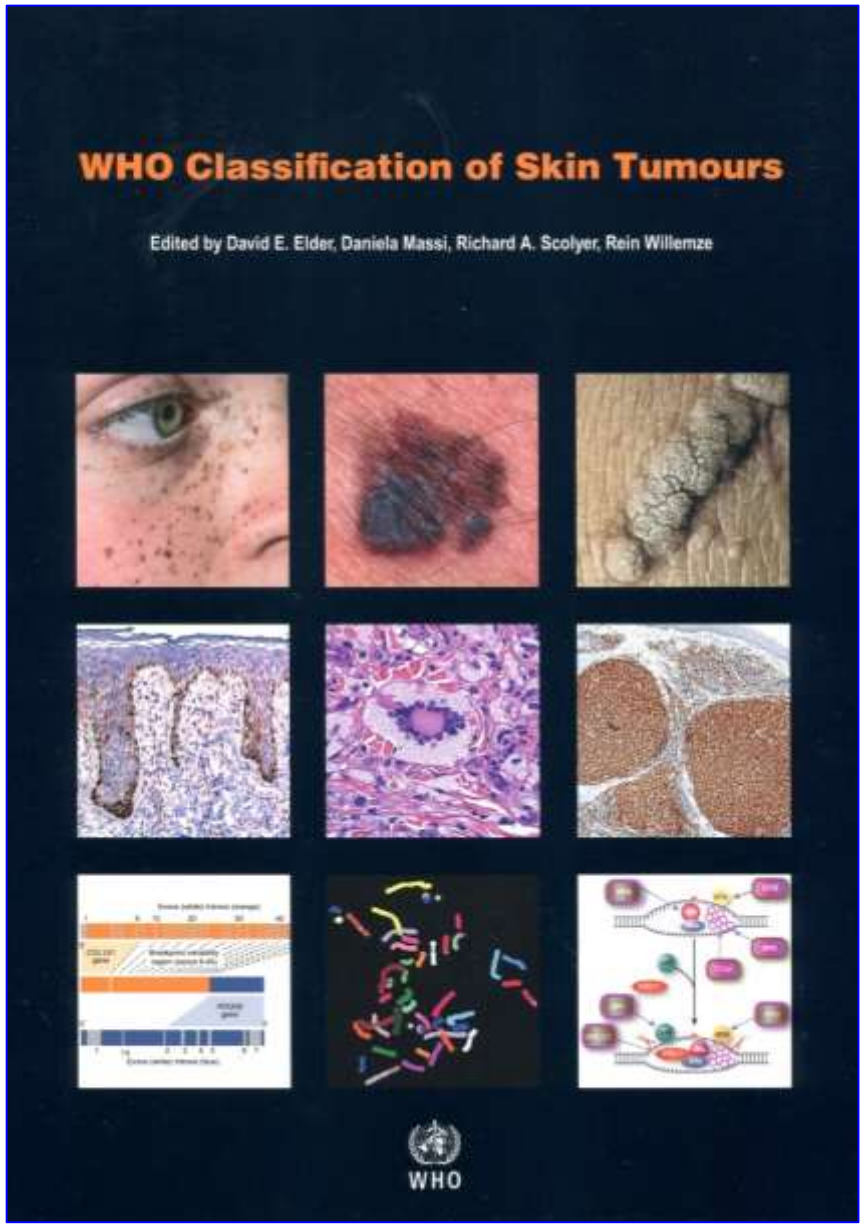
Contents

Other classifications fall far behind that standard. In the current “WHO Classification of Skin Tumours,” no word is wasted on principles of classification in biology. Hence, it comes as no surprise



Contents

that different stages of the same entity are assorted to different categories, such as so-called “carcinoma precursors” and “squamous cell carcinoma,”



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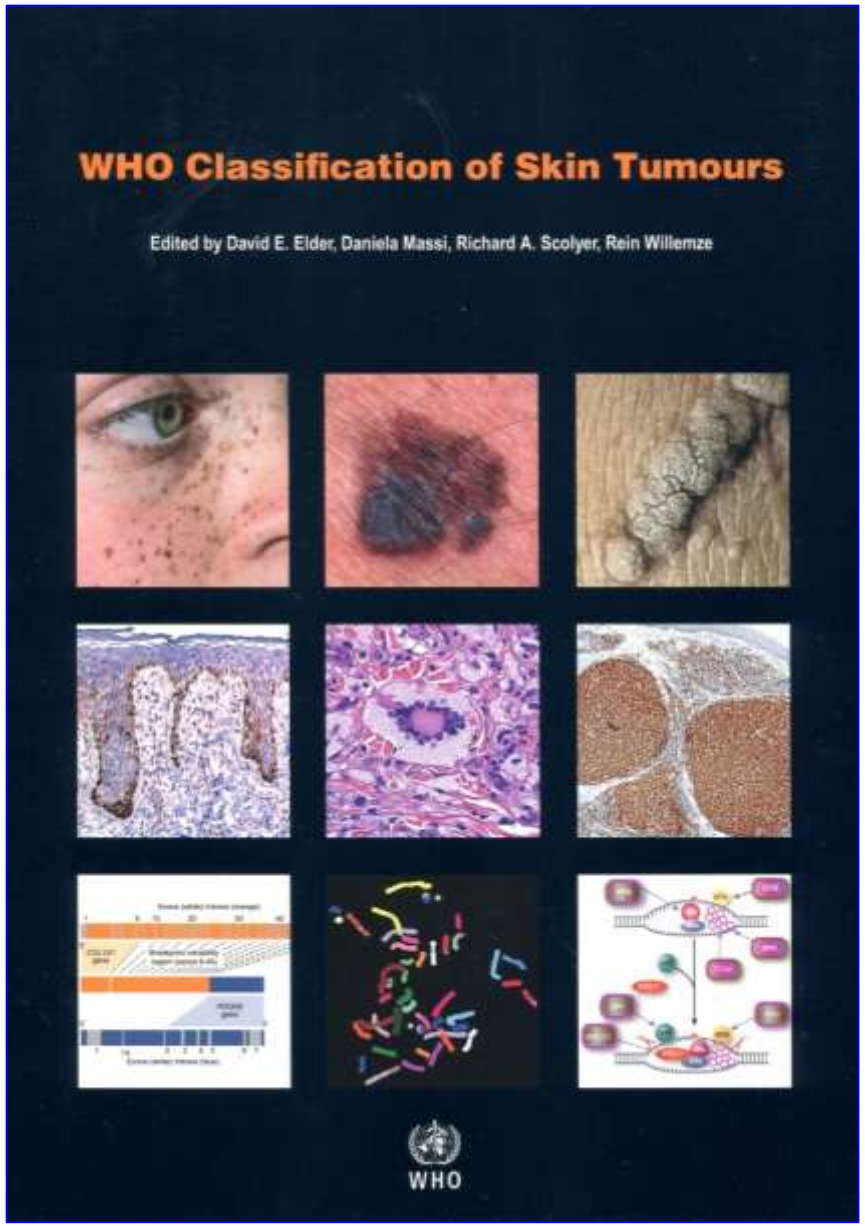
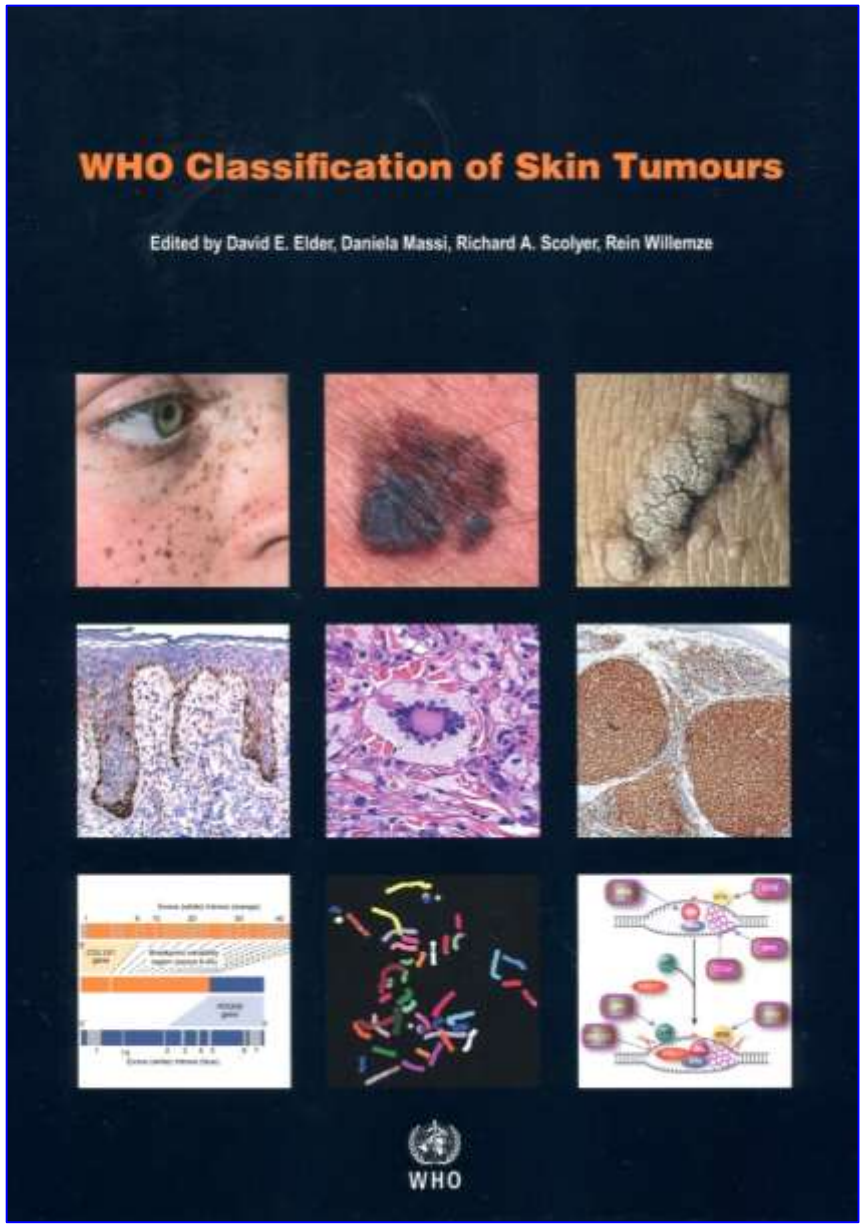
categories are not mutually exclusive, such as “nodular basal cell carcinoma” and “pigmented basal cell carcinoma” (as if a nodular basal-cell carcinoma could not be pigmented),



Contents

and all kinds of transitions are allowed, such as *“dysplastic naevus”*



Contents

Dysplastic naevi are intermediate between common acquired naevi and radial-growth-phase melanoma.

Elder DE et al., 2018

which is said to be *"intermediate between common acquired naevi and radial-growth-phase melanoma."*

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

	Low UV radiation exposure / CSD				High UV radiation exposure / CSD	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma / SSM				High-CSD melanoma / LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate / low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate / high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS	*BAP1*-inactivated melanocytoma / MELTUMP	Deep penetrating melanocytoma / MELTUMP	PEM / MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma / SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	***BRAF* p.V600E** or ***NRAS*** ; *TERT*; *CDKN2A*; *TP53*; *PTEN*	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS***; ***BRAF* (non-p.V600E)**; ***KIT***; or *NF1* ; *TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET* ; *TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11*

BIN, *BAP1*-inactivated naevus; **BN**, blue naevus; **CBN**, cellular blue naevus; **CN**, congenital naevus; **CSD**, cumulative sun damage; **DPN**, deep penetrating naevus; **IAMP**, intraepidermal atypical melanocytic proliferation; **IAMPUS**, intraepidermal atypical melanocytic proliferation of uncertain significance; **IMP**, intraepidermal melanocytic proliferation without atypia; **LMM**, lentigo maligna melanoma; low / high-CSD melanoma, melanoma in skin with a low / high degree of cumulative sun damage; **MELTUMP**, melanocytic tumour of uncertain malignant potential; **MIS**, melanoma in situ; **PEM**, pigmented epithelioid melanocytoma; **SSM**, superficial spreading melanoma; **STUMP**, spitzoid tumour of uncertain malignant potential; **UV**, ultraviolet; **VGP**, vertical growth phase (tumorigenic and/or mitogenic melanoma).

Those massive shortcomings present themselves in modern apparel. In the chapter on melanocytic neoplasms, various genetic alterations are listed that correlate with so-called “pathways” of melanoma, the most important distinction being between melanomas in skin with low cumulative sun-damage and with high cumulative sun-damage.

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

	Low UV radiation exposure / CSD				High UV radiation exposure / CSD	
Pathway						III
Endpoint of pathway						Desmoplastic melanoma
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Malignant neoplasms						Desmoplastic melanoma
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ORIGINAL ARTICLE

N Engl J Med 2005; 353: 2135

Distinct Sets of Genetic Alterations in Melanoma

John A. Curtin, Ph.D., Jane Fridlyand, Ph.D., Toshiro Kageshita, M.D., Hetal N. Patel, M.S., Klaus J. Busam, M.D., Heinz Kutzner, M.D., Kwang-Hyun Cho, M.D., Setsuya Aiba, M.D., Ph.D., Eva-Bettina Bröcker, M.D., Philip E. LeBoit, M.D., Dan Pinkel, Ph.D., and Boris C. Bastian, M.D.

ABSTRACT

BACKGROUND

Exposure to ultraviolet light is a major causative factor in melanoma, although the relationship between risk and exposure is complex. We hypothesized that the clinical heterogeneity is explained by genetically distinct types of melanoma with different susceptibility to ultraviolet light.

From the Comprehensive Cancer Center (J.A.C., J.F., H.N.P., D.P., B.C.B.) and the Departments of Epidemiology and Biostatistics (J.F.) and Dermatology and Pathology (P.E.L., B.C.B.), University of California, San Francisco, San Francisco; the Depart-

Those categories have been introduced in 2005 based on the hypothesis that *"the clinical heterogeneity is explained by genetically distinct types of melanoma with different susceptibility to ultraviolet light."* Indeed, BRAF mutated melanomas were found to be more common in the absence than in the presence of marked solar elastosis.

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

	Low UV radiation exposure / CSD				High UV radiation exposure / CSD	
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Mutant BRAF
78% vs. 10%

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N Engl J Med 2005; 353: 2135

OPEN ACCESS Freely available online — PLoS MEDICINE

2008; 5: e120

Improving Melanoma Classification by Integrating Genetic and Morphologic Features

Amaya Viros[1], **Jane Fridlyand**[2,3], **Juergen Bauer**[1], **Konstantin Lasithiotakis**[4], **Claus Garbe**[4], **Daniel Pinkel**[2,5], **Boris C. Bastian**[1,2,6*]

1 Department of Dermatology, University of California San Francisco, San Francisco, California, United States of America, 2 University of California San Francisco (UCSF) Comprehensive Cancer Center, University of California San Francisco, San Francisco, California, United States of America, 3 Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, United States of America, 4 Department of Dermatology, University of Tübingen, Tübingen, Germany, 5 Department of Laboratory Medicine, University of California San Francisco, San Francisco, California, United States of America, 6 Department of Pathology, University of California San Francisco, San Francisco, California, United States of America

Funding: Supported by grants from the National Cancer Institute (P01 CA025874, R01 CA094963). The funding agency did not have a role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Academic Editor: Jonathan Rees, University of Edinburgh, United Kingdom

ABSTRACT

Background

In melanoma, morphology-based classification systems have not been able to provide relevant information for selecting treatments for patients whose tumors have metastasized. The recent identification of causative genetic alterations has revealed mutations in signaling pathways that offer targets for therapy. Identifying morphologic surrogates that can identify patients whose tumors express such alterations (or functionally equivalent alterations) would be clinically useful for therapy stratification and for retrospective analysis of clinical trial data.

BIN, *BAP1*-inactivated naevus; **BN**, blue naevus; **CBN**, cellular blue naevus; **CN**, congenital naevus; **CSD**, cumulative sun damage; **DPN**, deep penetrating naevus; **IAMP**, intraepidermal atypical melanocytic proliferation; **IAMPUS**, intraepidermal atypical melanocytic proliferation of uncertain significance; **IMP**, intraepidermal melanocytic proliferation without atypia; **LMM**, lentigo maligna melanoma; low / high-CSD melanoma, melanoma in skin with a low / high degree of cumulative sun damage; **MELTUMP**, melanocytic tumour of uncertain malignant potential; **MIS**, melanoma in situ; **PEM**, pigmented epithelioid melanocytoma; **SSM**, superficial spreading melanoma; **STUMP**, spitzoid tumour of uncertain malignant potential; **UV**, ultraviolet; **VGP**, vertical growth phase (tumorigenic and/or mitogenic melanoma).

Subsequently, other morphologic features were studied with respect to the BRAF mutation status, and a correlation was found for some variables,

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

	Low UV radiation exposure / CSD				High UV radiation exposure / CSD	
Pathway						III
Endpoint of pathway						Desmoplastic melanoma
Benign neoplasms (naevi)						? IMP
Intermediate / low-grade dysplasias and melanocytomas						? IAMP/dysplasia
Intermediate / high-grade dysplasias and melanocytomas						MIS
Malignant neoplasms						Desmoplastic melanoma
Common mutations[a,b]	***BRAF* p.V600E** or ***NRAS*** *TERT*; *CDKN2A*; *TP53*; *PTEN*	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS***; ***BRAF* (non-p.V600E)**; ***KIT***; or ***NF1*** *TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET* *TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11*

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2008; 5: e120

Improving Melanoma Classification by Integrating Genetic and Morphologic Features

Amaya Viros[1], Jane Fridlyand[2,3], Juergen Bauer[1], Konstantin Lasithiotakis[4], Claus Garbe[4], Daniel Pinkel[2,5], Boris C. Bastian[1,2,6*]

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Competing Interests … have declared that n… interests exist.

Academic Editor: Jo… University of Edinbur… Kingdom

- increased upward migration and nest formation of intraepidermal melanocytes
- thickening of the involved epidermis
- sharper demarcation to the surrounding skin
- larger, rounder, and more pigmented tumor cells

namely, *"increased upward migration and nest formation of intraepidermal melanocytes, thickening of the involved epidermis, … sharper demarcation to the surrounding skin,"* and *"larger, rounder, and more pigmented tumor cells."* However, though significant statistically, those morphologic features were poorer predictors of BRAF mutation status than the age of the patients.

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

	Low UV radiation exposure/CSD				High UV radiation exposure/CSD	
Pathway						III
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Intermediate/low-grade dysplasias and melanocytomas						? IAMP/dysplasia
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Common mutations[a,b]	***BRAF* p.V600E** or ***NRAS*** ***TERT*; *CDKN2A*; *TP53*; *PTEN***	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF*, *MAP2K1*,** or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS*; *BRAF* (non-p.V600E); *KIT*;** or ***NF1*** ***TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1***	***NF1*; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET*** ***TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11***

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- We identified age < 55 y as the single most predictive factor of BRAF mutation
- The WHO categories [SSM, LMM] were not independently associated with BRAF mutation status

The authors *"identified age < 55 y as the single most predictive factor of BRAF mutation."* They also noted that *"the WHO categories,"* i.e., superficial spreading and lentigo maligna melanoma, *"were not independently associated with BRAF mutation status."*

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

	Low UV radiation exposure / CSD				High UV radiation exposure / CSD	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma / SSM				High-CSD melanoma / LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate / low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate / high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS	*BAP1*-inactivated melanocytoma / MELTUMP	Deep penetrating melanocytoma / MELTUMP	PEM / MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma / SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	***BRAF* p.V600E** or ***NRAS*** ; *TERT*; *CDKN2A*; *TP53*; *PTEN*	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS***; ***BRAF* (non-p.V600E)**; ***KIT***; or *NF1*; *TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET*; *TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11*

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Nonetheless, those categories are used as synonyms for melanomas with low and high cumulative sun damage in the current WHO classification.

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

	Low UV radiation exposure / CSD				High UV radiation exposure / CSD	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma / SSM				High-CSD melanoma / LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate / low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate / high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS				Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma / SSM (VGP)				LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	***BRAF* p.V600E** or ***NRAS***				***NRAS*; *BRAF* (non-p.V600E); *KIT*;** or ***NF1***	***NF1*; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET***
	TERT; *CDKN2A*; *TP53*; *PTEN*				*TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	*TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11*

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Hence, the emperor suddenly appears in new clothes, with a royal mantle of genetic alterations. Let us briefly look at his original outfit.

Melanocytic tumours in intermittently sun-exposed skin

Low-CSD melanoma (superficial spreading melanoma)

Duncan L.M.
Bastian B.C.
Elder D.E.
Mihm M.C. Jr

Definition
Low-CSD melanoma – melanoma in skin with a low degree of cumulative sun damage (CSD) as assessed by the degree of solar elastosis – is characterized by pagetoid and/or lentiginous intraepidermal components [492,493]; both of these major patterns are encompassed by the term "superficial spreading melanoma (SSM)". Melanomas arising via other pathways (e.g. melanoma arising in blue naevus) can occasionally also occur in low-CSD skin and should be interpreted accordingly.

ICD-O code 8743/3

Synonyms
Superficial spreading melanoma; non-CSD melanoma

Epidemiology
Low-CSD melanomas/SSMs account for nearly two thirds of cases occurring in lighter-skinned people (Fitzpatrick skin type I–III), and they are significantly less common in darker-skinned people. Males and females are affected similarly.

Etiology
Low-CSD melanoma/SSM is epidemiologically linked to sun exposure, and genomic analyses have revealed a high mutation burden with an ultraviolet (UV) radiation mutation signature [1094]. Repeated sunburns in childhood and intermittent sun exposure throughout life are associated with an increased risk of developing SSM. Tanning bed use has been linked to an increased rate of melanoma in young women [1508].

Localization
Low-CSD melanoma/SSM can occur at any cutaneous site, but is most common in locations with intermittent sun exposure, including women's legs and men's backs and shoulders.

Fig. 2.04 Superficial spreading melanoma. Th… has a radial-growth-phase component (plaque… dominantly tan, at the upper right of the lesion)… morigenic vertical growth phase (raised, pred… black in this example).

Clinical features
In situ, low-CSD melanoma/SSM… as a pigmented macule with an… lar outline; with the onset of in… a papule or plaque develops. T… ders of SSM are usually sharply… ited from the surrounding sk… may be poorly defined. The pig… tion is quite variable; multiple … of brown are often seen, rangin… tan to nearly black. There may b… areas corresponding to regressi…

red foci correlate with increased vascularity and inflammation. Occasionally, the melanoma may be amelanotic and mimic a keratinocytic neoplasm, but more commonly, pigment is present (often to a marked degree). The radial growth phase (RGP) may reach >1 cm in diameter before developing an invasive component. Dermal invasion often

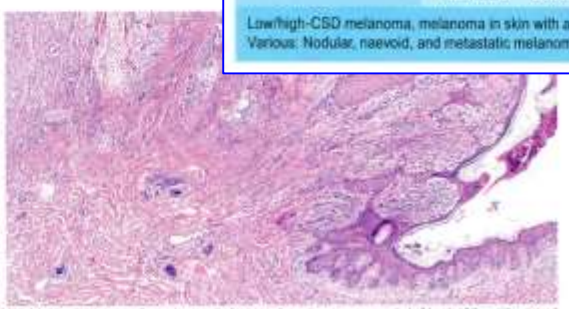

Fig. 2.05 Superficial spreading melanoma. Individual cells and nests are present at all levels of the epidermis and extend as a shoulder beyond the invasive dermal tumour. A benign naevus is present in the epidermis and dermis (lower right).

Table 2.01 Classification of melanoma

Melanomas arising in sun-exposed skin	Pathway I:	Low-CSD melanoma/superficial spreading melanoma
	Pathway II:	High-CSD melanoma/lentigo maligna melanoma
	Pathway III:	Desmoplastic melanoma
Melanomas arising at sun-shielded sites or without known etiological associations with UV radiation exposure	Pathway IV:	Malignant Spitz tumour (Spitz melanoma)
	Pathway V:	Acral melanoma
	Pathway VI:	Mucosal melanoma
	Pathway VII:	Melanoma arising in congenital naevus
	Pathway VIII:	Melanoma arising in blue naevus
	Pathway IX:	Uveal melanoma
Low/high-CSD melanoma, melanoma in skin with a low/high degree of cumulative sun damage		
Various: Nodular, naevoid, and metastatic melanomas.		

Melanocytic tumours in chronically sun-exposed skin

Lentigo maligna melanoma

Elder D.E.
Bastian B.C.
Kim J.
Massi D.
Mihm M.C. Jr
Scolyer R.A.
Wood B.A.

Definition
High-CSD melanomas – melanomas in skin with a high degree of cumulative sun damage (CSD) as evidenced by severe solar elastosis – have distinctive clinical and genetic features. Lentigo maligna melanoma (LMM) is a type of high-CSD melanoma characterized by a lentiginous in situ component called lentigo maligna

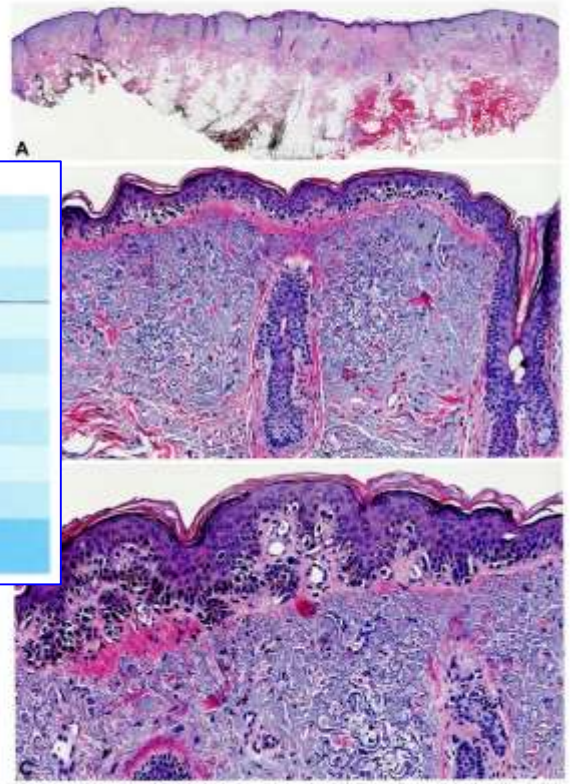

Fig. 2.47 Lentigo maligna melanoma. Radial-growth-phase lesions usually present as a variegated patch/plaque in the skin; unlike in superficial spreading melanoma, the border is poorly defined in some areas and non-palpable.

Fig. 2.48 Lentigo maligna. **A** Broad resection specimen with a pink biopsy site scar, extensive solar elastosis, and irregularities of the epidermal contour including patchy rete ridge effacement. **B** This field shows the so-called classic pattern, with continuous basal (lentiginous) proliferation of uniformly atypical naevoid to epithelioid melanocytes. **C** Another field shows the dysplastic naevus-like (or naevoid lentigo maligna) pattern. Although this single field is not diagnostic of lentigo maligna, it is part of the larger lesion illustrated in panels A and B.

The two types of melanoma presented as the first and most important "pathways" in the current WHO classification, superficial spreading melanoma and lentigo maligna melanoma, were described by Wallace H. Clark in 1969.


Melanocytic tumours in intermittently sun-exposed skin

Low-CSD melanoma
(superficial spreading melanoma)

Duncan L.M.
Bastian B.C.
Elder D.E.
Mihm M.C. Jr

Definition
Low-CSD melanoma – melanoma in skin with a low degree of cumulative sun damage (CSD) as assessed by the degree of solar elastosis – is characterized by pagetoid and/or lentiginous intraepidermal components [492,493]; both of these major patterns are encompassed by the term "superficial spreading melanoma (SSM)". Melanomas arising via other pathways (e.g. melanoma arising in blue naevus) can occasionally also occur in low-CSD skin and should be interpreted accordingly.

ICD-O code 8743/3

Synonyms
Superficial spreading melanoma; non-CSD melanoma

Epidemiology
Low-CSD melanomas/SSMs account for nearly two thirds of cases occurring in lighter-skinned people (Fitzpatrick

Fig.2.04 Superficial spreading melanoma. T
has a radial-growth-phase component (plaqu
dominantly tan, at the upper right of the lesion
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Fig.2.05 Superficial spreading melanoma. A
extend as a shoulder beyond the invasive de
(lower right).

70 Melanocytic tumours

- arciform outline
- elevated surface
- striking variation of color
- more epithelioid melanocytes
- prominent pagetoid growth
- relatively uniform cells

[CANCER RESEARCH 29, 705–726, March 1969]

The Histogenesis and Biologic Behavior of Primary Human Malignant Melanomas of the Skin[1]

Wallace H. Clark, Jr.,[2] Lynn From, Evelina A. Bernardino, and Martin C. Mihm

Department of Pathology and Dermatology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114

SUMMARY

This paper describes the histogenesis of 3 forms of human malignant melanoma: superficial spreading melanoma, nodular melanoma, and lentigo maligna melanoma. A comparative analysis by computer of the biologic behavior and clinical characteristics of the different neoplasms has been done. An additional 60 tumors have been studied by serial block sectioning. Evidence is presented suggesting that superficial spreading melanoma and lentigo maligna melanoma (Hutchinson's melanotic freckle), though evolving at different rates, show a long period of superficial growth, followed by the relatively rapid appearance of nodules or deeper invasion within the primary lesion. This change in the nature of the primary lesion may be due to the appearance of one or more strains of cells of aggressive biologic potential. Thus the primary melanoma may exist for a relatively long period of time during which host selectional forces act to permit the growth of quite malignant strains of cells. It is these cells that seem to be capable of deeper growth. The subdivision of each of the forms of melanoma into 5 anatomic levels of invasion permits the accurate assignment of prognosis to each case. It is suggested that melanomas are tumors of the epidermal melanocytes and are not necessarily derived from melanocytic nevi. Each melanoma has a distinctive clinical appearance, even in its superficial and curable phases, and this appearance is the same whether or not the process arose in association with a melanocytic nevus.

INTRODUCTION

This paper describes 3 different malignant tumors affecting the human epidermal melanocytic system. These neoplastic processes are described under the terms superficial spreading melanoma, nodular melanoma, and lentigo maligna melanoma (Hutchinson's melanotic freckle or circumscribed precancerous melanosis of Dubreuilh). Each of these tumors has a recognizable appearance in the patient, distinctive microscopic characteristics, and to a certain extent unique fine structural features. The history of the evolution of each of the primary neoplasms is different, and each has a predictable biologic behavior. Furthermore, within each kind of tumor, behavior may be accurately predicted by the depth of invasion of the neoplastic cells. Finally, various clinical characteristics such as location and age also serve to distinguish the various melanomas.

We shall also discuss the relationship of the junction nevus to malignant melanoma. It is our opinion that the junction nevus has no formal histogenetic relationship to malignant melanoma. Only in the bathing trunk nevus is there a high incidence of malignant melanoma and the tumors arising in these lesions are of no statistical importance in the overall problem of melanoma. We regard the majority of melanomas as malignant neoplasms of epidermal melanocytes. This pigment-synthesizing system has a specific distribution throughout the normal epidermis (27, 39, 40), and the cells of the system may be found in a variety of cutaneous lesions including the intraepidermal component of various nevi. Regardless of where melanocytes are located, in normal skin, in freckles, in pigmented nevi, or in other benign lesions, the etiologic factors, as yet largely unknown, that cause melanoma can act upon these melanocytes. The concept of the junction nevus as a premalignant lesion seems to have obscured the fact that most malignant melanomas pass through a long phase of superficial growth during which the process differs in appearance from junctional nevi and is easily recognized on clinical examination.

MATERIALS AND METHODS

This report is based upon the study of 3 series of malignant melanomas observed at the Massachusetts General Hospital. The first series consisted of 96 cases observed prior to Jan. 1, 1958. These cases were selected solely on the basis of the availability of technically satisfactory histologic material of the primary neoplasm and on adequate followup information. The histogenetic concepts underlying much of the present report were formulated through the investigation of the first series of 96 melanomas and have been previously reported in detail (5). These 96 cases have been incorporated with the second series of 113 cases observed between January 1958 and October 1965, and subjected to statistical analysis by computer. The third series of melanomas consists of 60 cases observed from October 1965 through May 1968, which have been studied in detail, clinically and morphologically, but not incorporated into the statistical study because of short follow-

[1]Supported by grants from the National Cancer Institute CA-06221, the Massachusetts Division of the American Cancer Society, and the Damon Runyon Fund.

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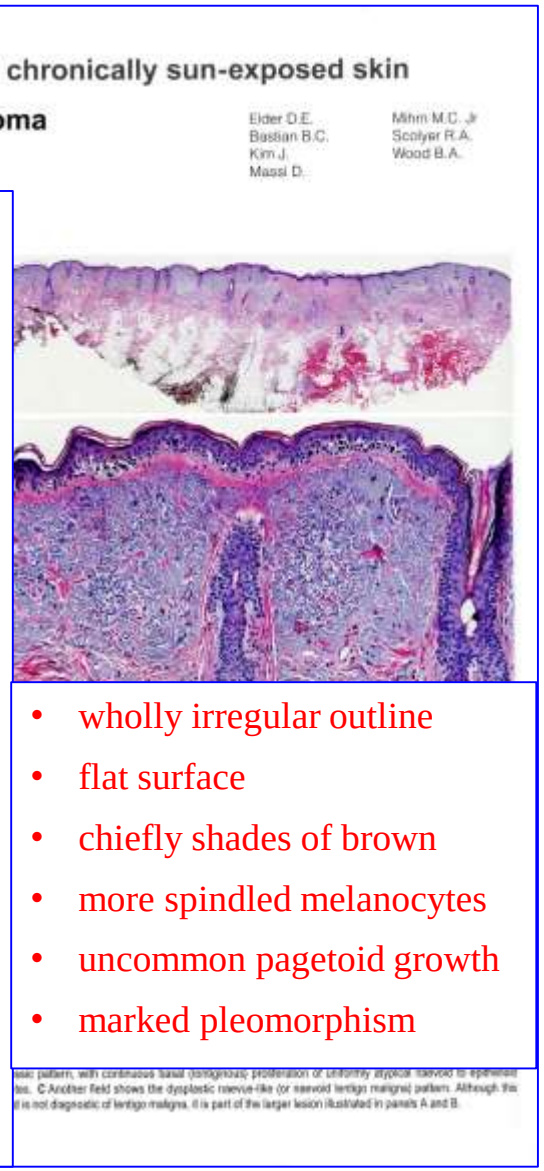
Received July 8, 1968; accepted November 4, 1968.


Melanocytic tumours in chronically sun-exposed skin

Lentigo maligna melanoma

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- wholly irregular outline
- flat surface
- chiefly shades of brown
- more spindled melanocytes
- uncommon pagetoid growth
- marked pleomorphism

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In his seminal article, Clark listed the following distinguishing features: arciform vs. wholly irregular outline, elevated vs. flat surface, striking variation of color vs. chiefly shades of brown, prominent vs. uncommon pagetoid growth, and relatively uniform appearance of cells vs. marked pleomorphism.

Those criteria were modified repeatedly; some were dropped and others added, namely, uncommon vs. common regression, relatively sharp vs. poor circumscription, epidermal hyperplasia vs. atrophy, and absence vs. presence of solar elastosis.

Melanocytic tumours in intermittently sun-exposed skin

Low-CSD melanoma (superficial spreading melanoma)

Duncan L.M.
Bastian B.C.
Elder D.E.
Mihm M.C. Jr

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Fig.2.05 Superficial spreading melanoma. (
extend as a shoulder beyond the invasive de
(lower right).

70 Melanocytic tumours

- more epithelioid melanocytes
- prominent pagetoid growth
- relatively uniform cells
- regression uncommon
- relatively sharp circumscription
- epidermal hyperplasia
- no solar elastosis

[CANCER RESEARCH 29, 705–726, March 1969]

The Histogenesis and Biologic Behavior of Primary Human Malignant Melanomas of the Skin[1]

Wallace H. Clark, Jr.,[2] **Lynn From, Evelina A. Bernardino, and Martin C. Mihm**

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INTRODUCTION

This paper describes 3 different malignant tumors affecting the human epidermal melanocytic system. These neoplastic processes are described under the terms superficial spreading melanoma, nodular melanoma, and lentigo maligna melanoma (Hutchinson's melanotic freckle or circumscribed precancerous melanosis of Dubreuilh). Each of these tumors has a recognizable appearance in the patient, distinctive microscopic characteristics, and to a certain extent unique fine structural features. The history of the evolution of each of the primary neoplasms is different, and each has a predictable biologic behavior. Furthermore, within each kind of tumor, behavior may be accurately predicted by the depth of invasion of the neoplastic cells. Finally, various clinical characteristics such as location and age also serve in distinguishing the various melanomas.

We shall also discuss the relationship of the junction nevus to malignant melanoma. It is our opinion that the junction nevus has no formal histogenetic relationship to malignant melanoma. Only in the bathing trunk nevus is there a high incidence of malignant melanoma and the tumors arising in these lesions are of no statistical importance in the overall problem of melanoma. We regard the majority of melanomas as malignant neoplasms of epidermal melanocytes. This pigment-synthesizing system has a specific distribution throughout the normal epidermis (27, 39, 40), and the cells of the system may be found in a variety of cutaneous lesions including the intraepidermal component of various nevi. Regardless of where melanocytes are located, in normal skin, in freckles, in pigmented nevi, or in other benign lesions, the etiologic factors, as yet largely unknown, that cause melanoma can act upon these melanocytes. The concept of the junction nevus as a premalignant lesion seems to have obscured the fact that most malignant melanomas pass through a long phase of superficial growth during which the process differs in appearance from junctional nevi and is easily recognized on clinical examination.

MATERIALS AND METHODS

This report is based upon the study of 3 series of malignant melanomas observed at the Massachusetts General Hospital. The first series consisted of 96 cases observed prior to Jan. 1, 1958. These cases were selected solely on the basis of the availability of technically satisfactory histologic material of the primary neoplasm and on adequate followup information. The histogenetic concepts underlying much of the present report were formulated through the investigation of the first series of 96 melanomas and have been previously reported in detail (5). These 96 cases have been incorporated with the second series of 113 cases observed between January 1958 and October 1965, and subjected to statistical analysis by computer. The third series of melanomas consists of 60 cases observed from October 1965 through May 1968, which have been studied in detail, clinically and morphologically, but not incorporated into the statistical study because of short follow-

[1]Supported by grants from the National Cancer Institute CA-06221, the Massachusetts Division of the American Cancer Society, and the Damon Runyon Fund.

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Received July 8, 1968; accepted November 4, 1968.

Melanocytic tumours in chronically sun-exposed skin

Lentigo maligna melanoma

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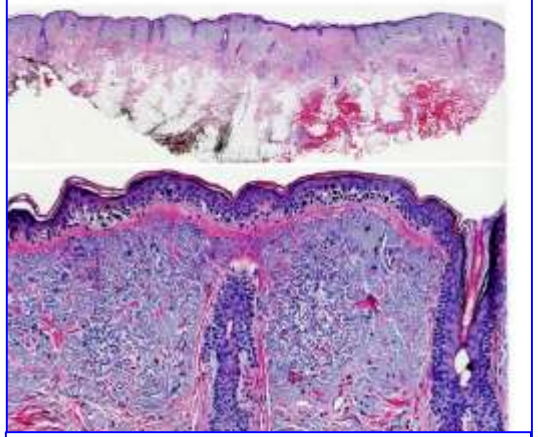
Bastian B.C.
Kim J.
Massi D.

Mihm M.C. Jr
Scolyer R.A.
Wood B.A.



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tes. C Another field shows the dysplastic naevus-like (or naevoid lentigo maligna) pattern. Although this
it is not diagnostic of lentigo maligna, it is part of the larger lesion illustrated in panels A and B.

- more spindled melanocytes
- uncommon pagetoid growth
- marked pleomorphism
- regression common
- poor circumscription
- epidermal atrophy
- solar elastosis

Melanocytic tumours in intermittently sun-exposed skin

Low-CSD melanoma (superficial spreading melanoma)

Duncan L.M.
Bastian B.C.
Elder D.E.
Mihm M.C. Jr

Definition
Low-CSD melanoma – melanoma in skin with a low degree of cumulative sun damage (CSD) as assessed by the degree of solar elastosis – is characterized by pagetoid and/or lentiginous intraepidermal components [492,493]; both of these major patterns are encompassed by the term "superficial spreading melanoma (SSM)". Melanomas arising via other pathways (e.g. melanoma arising in blue naevus) can occasionally also occur in low-CSD skin and should be interpreted accordingly.

ICD-O code 8743/3

Synonyms
Superficial spreading melanoma; non-CSD melanoma

Epidemiology
Low-CSD melanomas/SSMs account for nearly two thirds of cases occurring in lighter-skinned people (Fitzpatrick

Fig.2.04 Superficial spreading melanoma. T
has a radial-growth-phase component (plaque
dominantly tan, at the upper right of the lesion
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Clinical features
In situ, low-CSD melanoma/SSM
as a pigmented macule with ir
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70 Melanocytic tumours

- more epithelioid melanocytes
- prominent pagetoid growth
- relatively uniform cells
- regression uncommon
- relatively sharp circumscription
- epidermal hyperplasia
- no solar elastosis

288

Classification of Cutaneous Malignant Melanoma

A Reassessment of Histopathologic Criteria for the Distinction of Different Types

Wolfgang Weyers, M.D.[1]
Matthias Euler, M.D.[2]
Carlos Diaz-Cascajo, M.D.[1]
Wolf-Bernhard Schill, M.D.[2]
Matthias Bonczkowitz, M.D.[2]

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METHODS. Nine hundred fifteen melanomas were examined with regard to 72 parameters that are considered to be important for histopathologic diagnosis. The results were analyzed statistically with special attention to findings that have been reported to be characteristic of the four principle types of melanoma.

RESULTS. The histopathologic criteria advocated for the distinction of different types of melanoma were found not to correlate with one another. A logistic regression analysis did not detect any other repeatable constellation of morphologic findings that may reflect a distinct biologic subgroup.

CONCLUSIONS. The validity of the current classification of cutaneous malignant melanoma into four principle types could not be substantiated. Malignant melanoma may present with many different forms, but these forms appear to be part of a continuous spectrum rather than examples of distinct biologic entities. *Cancer* 1999;86:288–99. © 1999 American Cancer Society.

KEYWORDS: malignant melanoma, classification, nodular melanoma, superficial spreading melanoma, lentigo maligna melanoma, acral-lentiginous melanoma.

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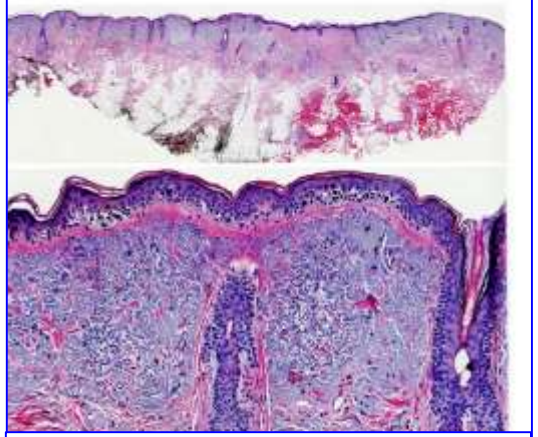

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Melanocytic tumours in intermittently sun-exposed skin

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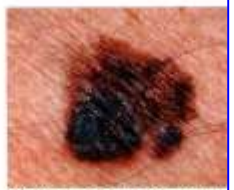

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26/830 (3.1%)

288

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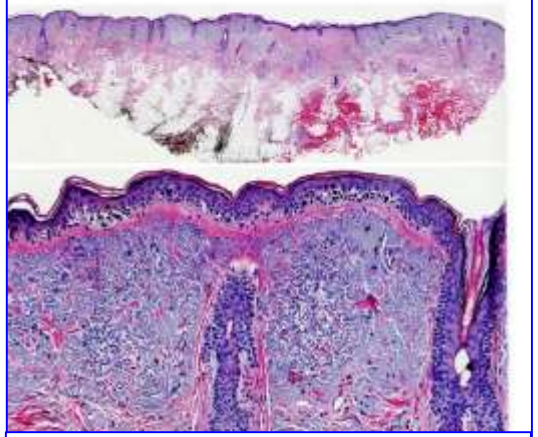

- more spindled melanocytes
- uncommon pagetoid growth
- epidermal atrophy
- solar elastosis

7/830 (0.7%)

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If only the four most commonly used criteria were considered, they were fulfilled for superficial spreading melanoma in 3.1% and for lentigo maligna melanoma in 0.7% of the cases.

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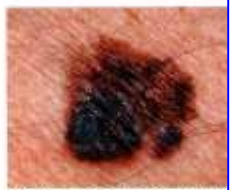

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181/830 (21%)

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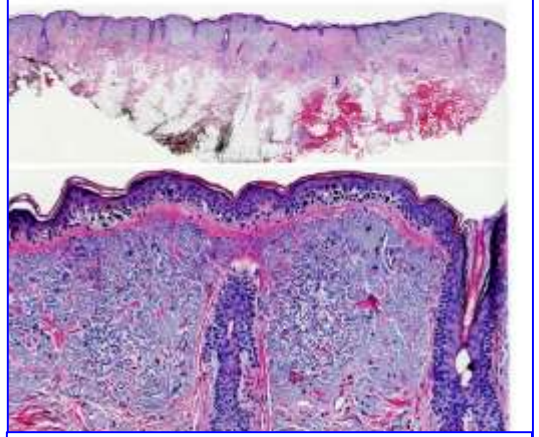

- uncommon pagetoid growth
- epidermal atrophy
- solar elastosis

46/830 (5.5%)

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The most common combination of three criteria for superficial spreading melanoma was noted in 21% and for lentigo maligna melanoma in 5.5% of cases. This corresponds to data from other studies,

including one by Clark and co-workers who concluded in 1984 that *"LMM is a rarity."*

Now this rarity

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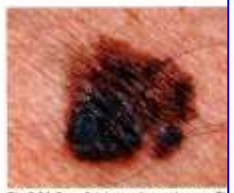

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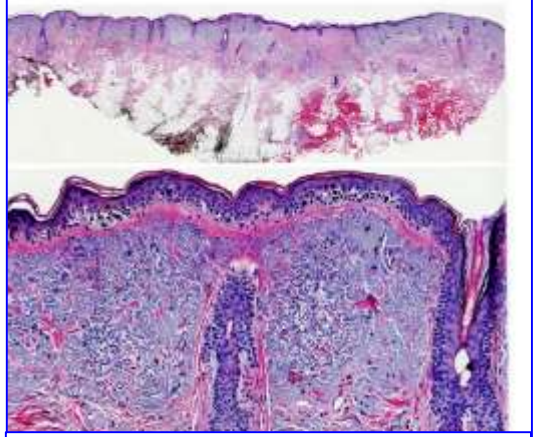
Lentigo Maligna Melanoma Has No Better Prognosis Than Other Types of Melanoma

J Clin Oncol 1984; 2: 994

By Howard K. Koh, Edna Michalik, Arthur J. Sober, Robert A. Lew, Calvin L. Day, Wallace Clark, Martin C. Mihm, Alfred W. Kopf, M. Scott Blois, and Thomas B. Fitzpatrick

We studied 48 patients with lentigo maligna melanoma (LMM) and compared the clinical stage I patients with non-LMM melanoma p... and thickness) to see if prog... no significant difference in r... between the two groups (P... low-up time of five years (67... months for non-LMM). In addition, a Cox multivariate analysis of the entire matched group showed that only thickness was significantly associated with death from melanoma (P = .0007) while histology ...nake a significant contribu... ...ggest that after accounting ...ss and site, LMM and non... ...osis and biologic behavior, ...held belief that LMM has a better prognosis than other forms of melanoma.

LMM is a rarity.



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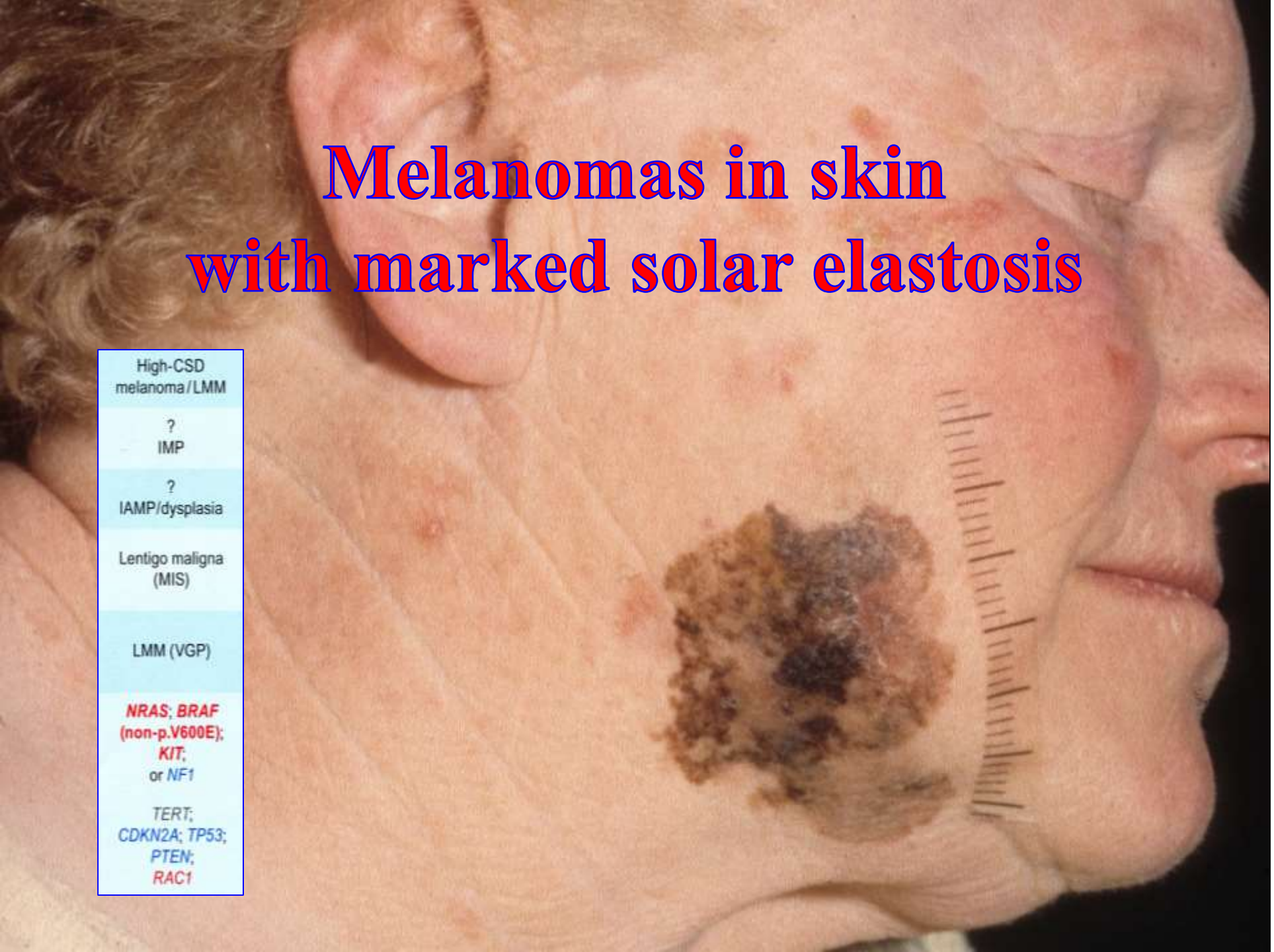
Melanomas in skin with marked solar elastosis



suddenly re-emerges as one of the “two major pathways” of melanoma and with a ostensibly characteristic genetic profile that, however, has been elaborated under consideration of solar elastosis alone. A closer look reveals that the genetic profile is not quite so characteristic.

Melanomas in skin with marked solar elastosis

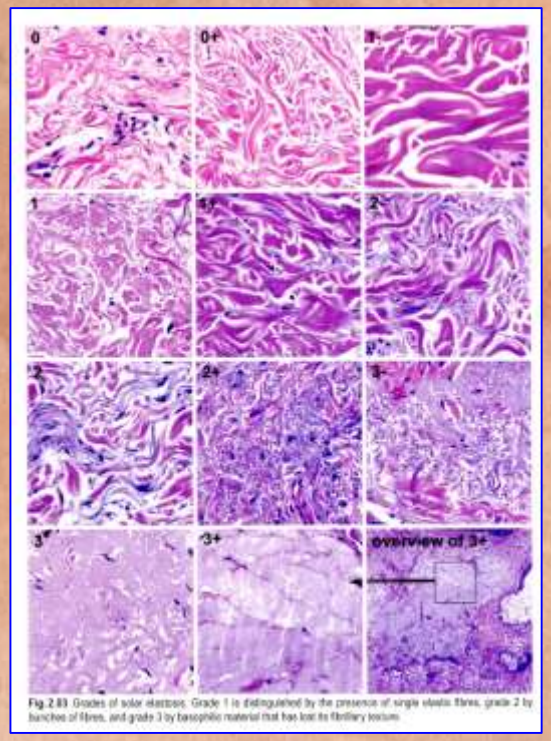
- BRAF mutations rare (~10%, BRAF V600K > BRAF V600E)
- inactivating NF1 mutations (~30%)
- activating KIT mutations (~10%)

Although BRAF mutations are rare, they have been found in 10% of cases, V600K mutations exceeding the more common V600E mutations. Inactivating NF1 mutations are said to be typical but are found in only 30% of cases, and KIT mutations in only 10%. Moreover, none of these and other genetic changes are specific but also found in other types of melanoma, e.g., KIT mutations in acral and mucosal melanomas. In short, genetic alterations do not suffice to define a distict type of melanoma, let alone a specific entity.

Melanomas in skin with marked solar elastosis

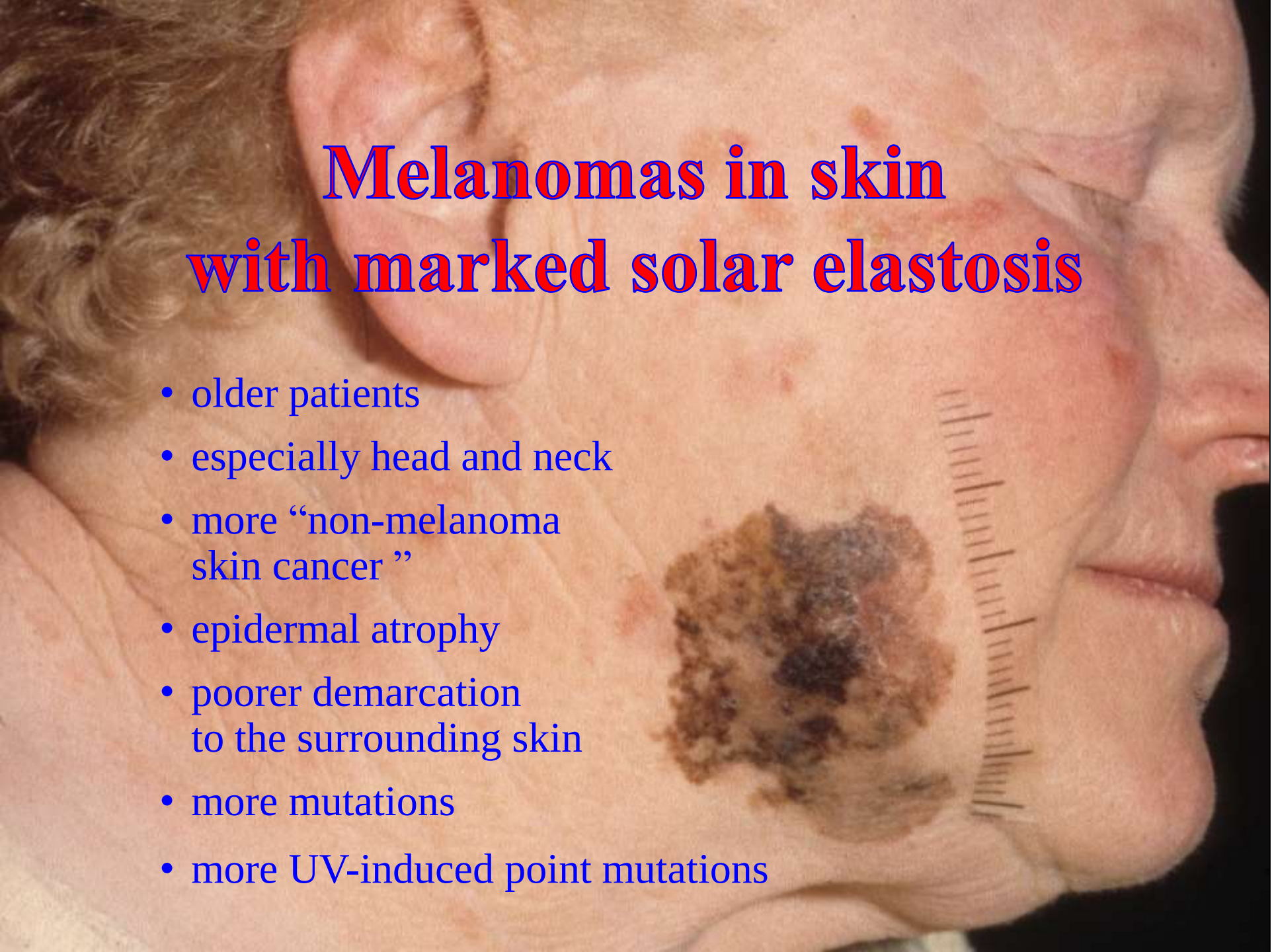
High-CSD melanoma / LMM
? IMP
? IAMP/dysplasia
Lentigo maligna (MIS)
LMM (VGP)
NRAS; *BRAF* (non-p.V600E); *KIT*; or *NF1*
TERT; *CDKN2A*; *TP53*; *PTEN*; *RAC1*

Pathway I:	Low-CSD melanoma/superficial spreading melanoma
Pathway II:	High-CSD melanoma/lentigo maligna melanoma



This is were marked solar elastosis comes into play as an additional defining factor.

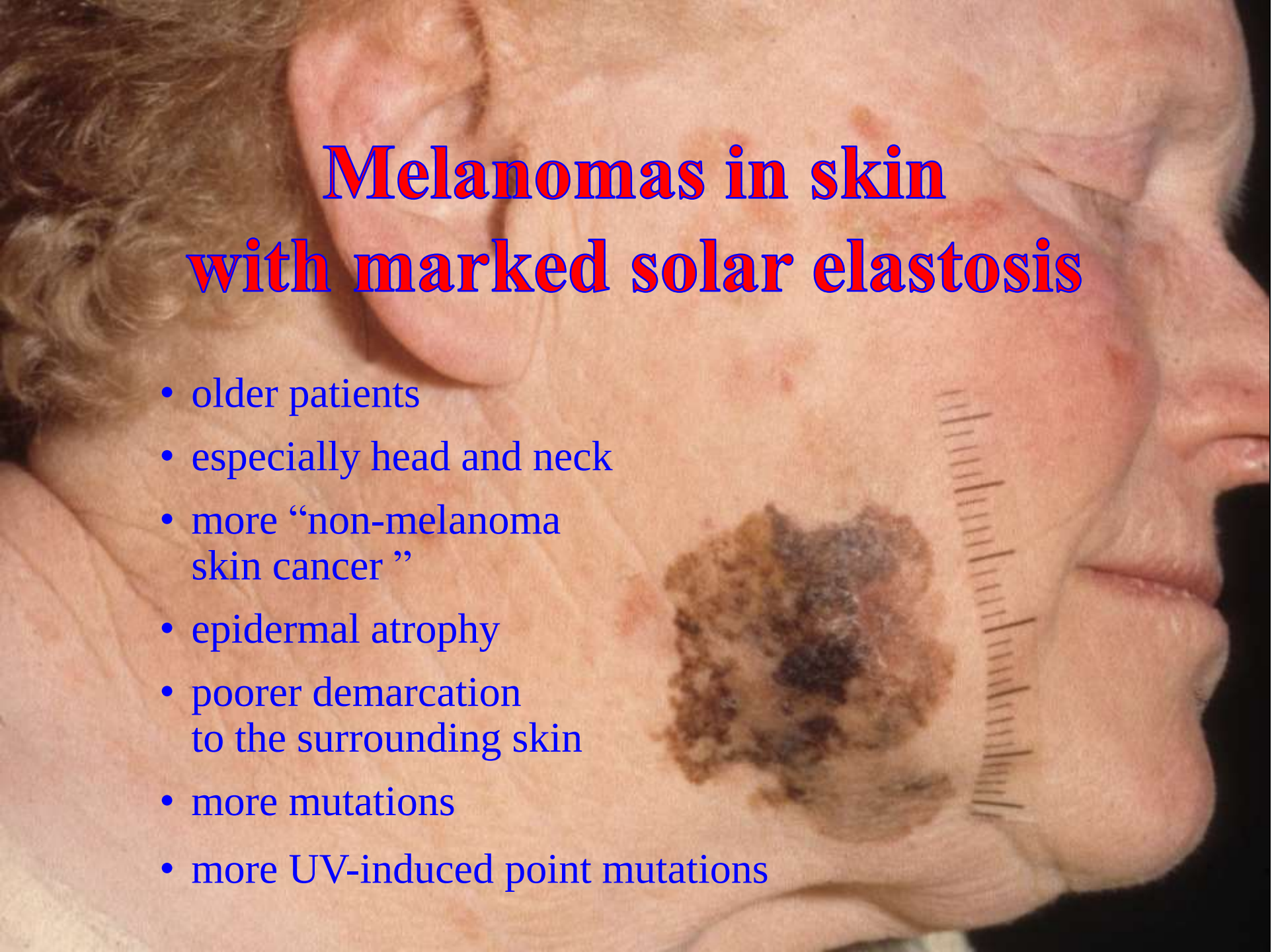
So how about solar elastosis? Evidently, it is a continuous variable ranging from absent to marked, as also conceded in the current WHO classification of melanoma. As such, it does not lend itself to the dichotomous distinction of low vs. high cumulative sun damage. If only melanomas with marked solar elastosis are considered, they are said to distinguish themselves by a characterized set of features.



Melanomas in skin with marked solar elastosis

- older patients
- especially head and neck
- more “non-melanoma skin cancer ”
- epidermal atrophy
- poorer demarcation to the surrounding skin
- more mutations
- more UV-induced point mutations

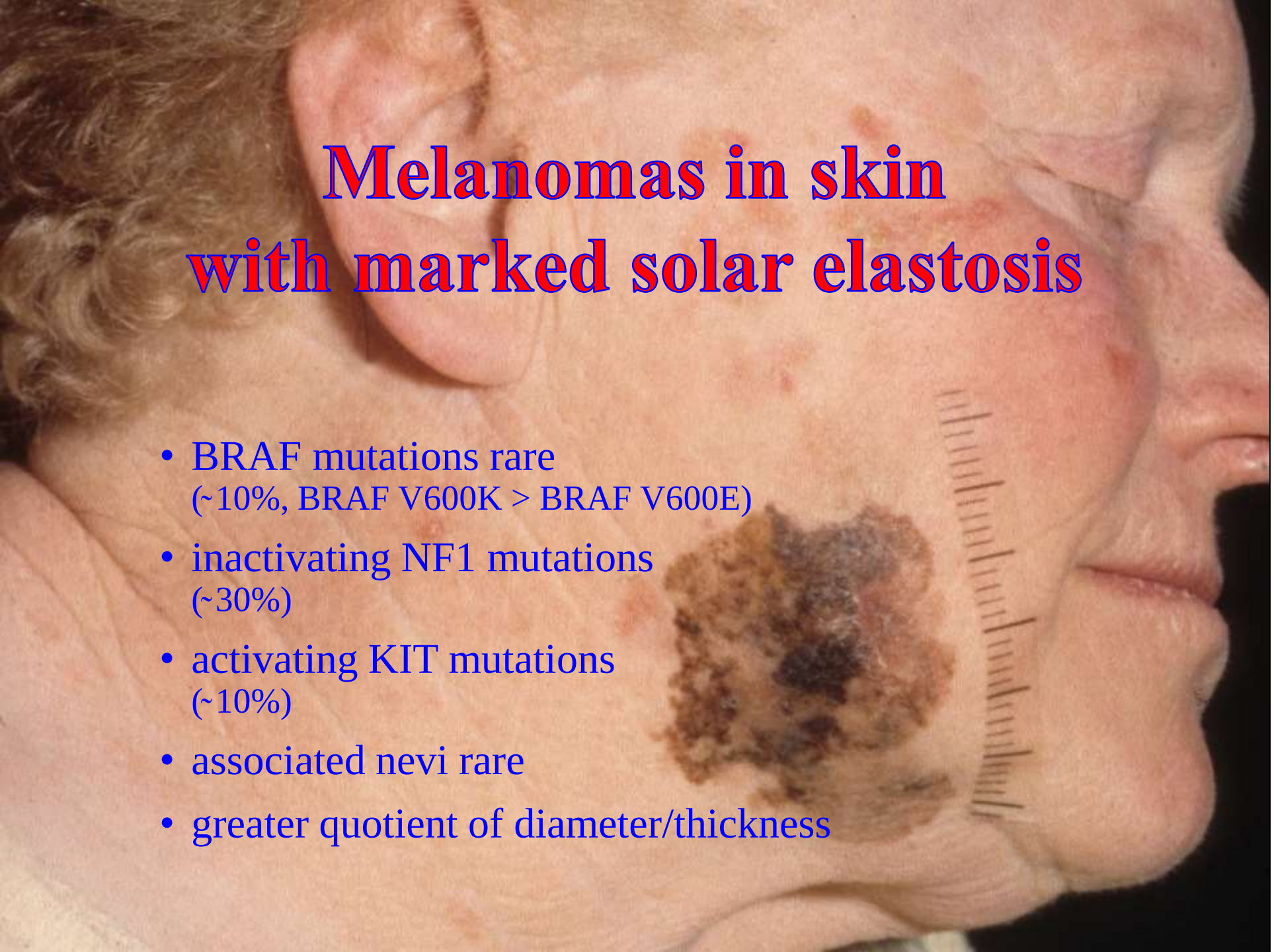
Patients are significantly older than those without marked solar elastosis, melanomas occur especially on the head and neck, they are associated more commonly with so-called “non-melanoma skin cancer,” they show epidermal atrophy, a poorer demarcation to the surrounding skin, more mutations, and, especially, more UV-induced point mutations. *All those ostensibly peculiar features are directly related to the definition.*



Melanomas in skin with marked solar elastosis

- older patients
- especially head and neck
- more “non-melanoma skin cancer ”
- epidermal atrophy
- poorer demarcation to the surrounding skin
- more mutations
- more UV-induced point mutations

Of course, patients with marked solar elastosis are significantly older because solar elastosis needs some time to develop; of course, melanomas are found chiefly on the head and neck and are associated more commonly with other types of UV-induced cancer; of course, the epidermis tends to be atrophic and the demarcation poor because of melanocytic hyperplasia in the surrounding sun-damaged skin; of course, there are UV-induced mutations. All of those features are expected in sun-damaged skin, whether or not there is a melanoma.



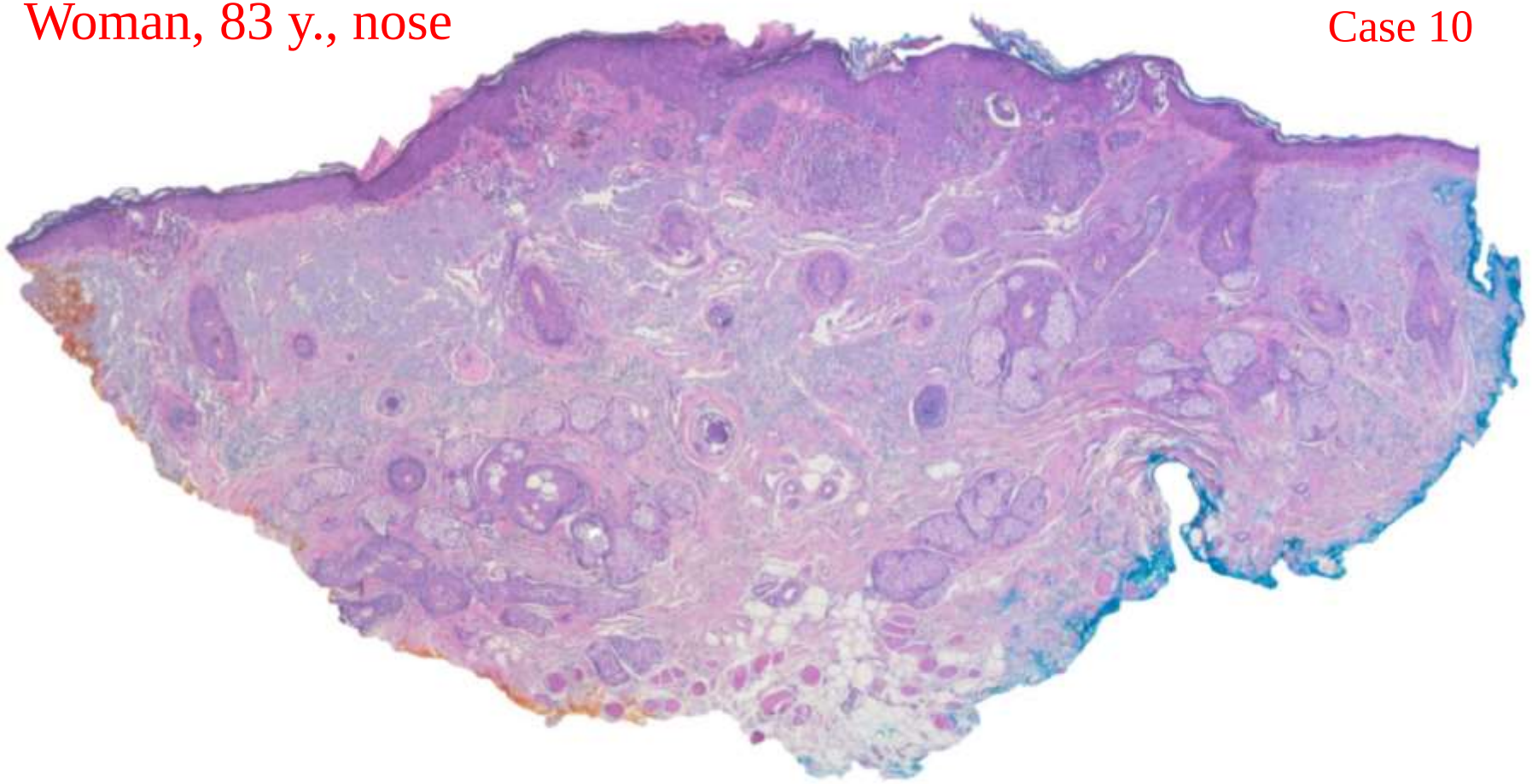
Melanomas in skin with marked solar elastosis

- BRAF mutations rare
  (~10%, BRAF V600K > BRAF V600E)
- inactivating NF1 mutations
  (~30%)
- activating KIT mutations
  (~10%)
- associated nevi rare
- greater quotient of diameter/thickness

There are also some peculiarities not explained readily by the definition, including some of the genetic findings and the rarity of associated nevi. In our own study we found a greater ratio of diameter through thickness in melanomas with marked solar elastosis, i.e., melanomas with the same thickness tended to be broader in sun-damaged skin. However, though significant statistically, this was only a tendency. As for all other variables, exceptions were too common for recognition of any distinct subtype.

Woman, 83 y., nose

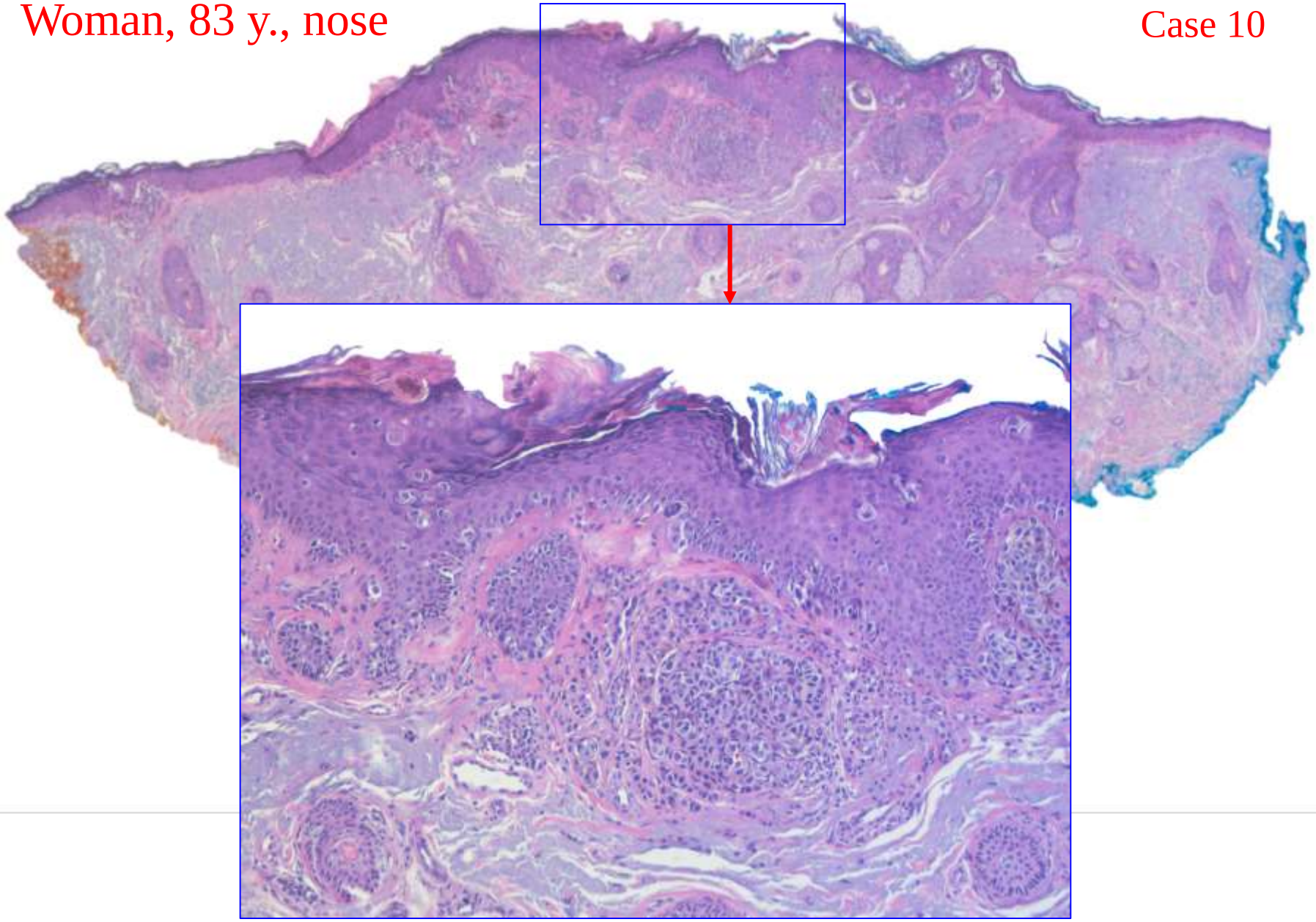
Case 10



As but one example, take case 10 of the self assessment, a melanoma from the nose of an 83 year-old woman. Because of marked solar elastosis, one may be prompted to classify it as “lentigo maligna melanoma,” but it is relatively thick in comparison to its small diameter.

Woman, 83 y., nose

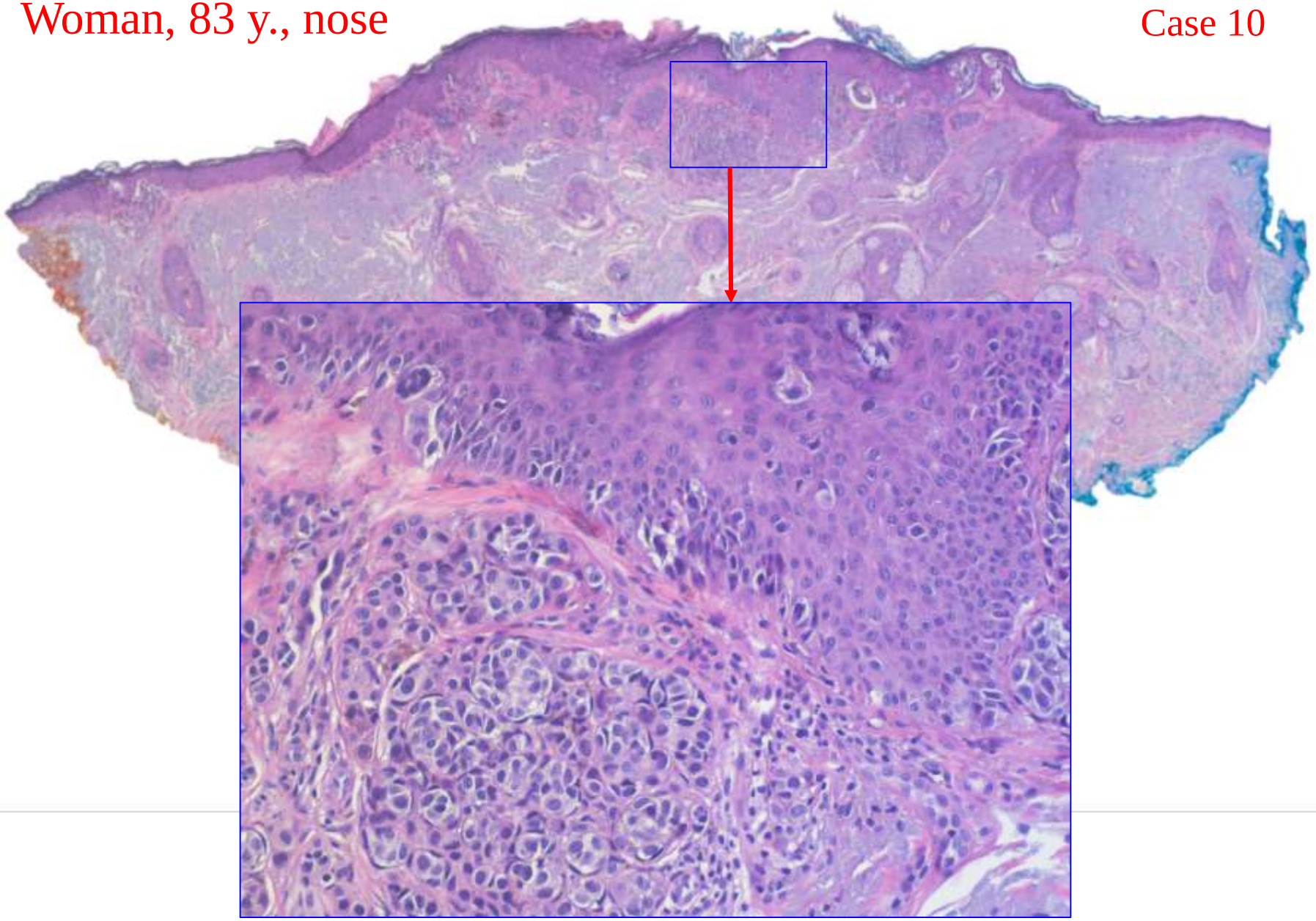
Case 10



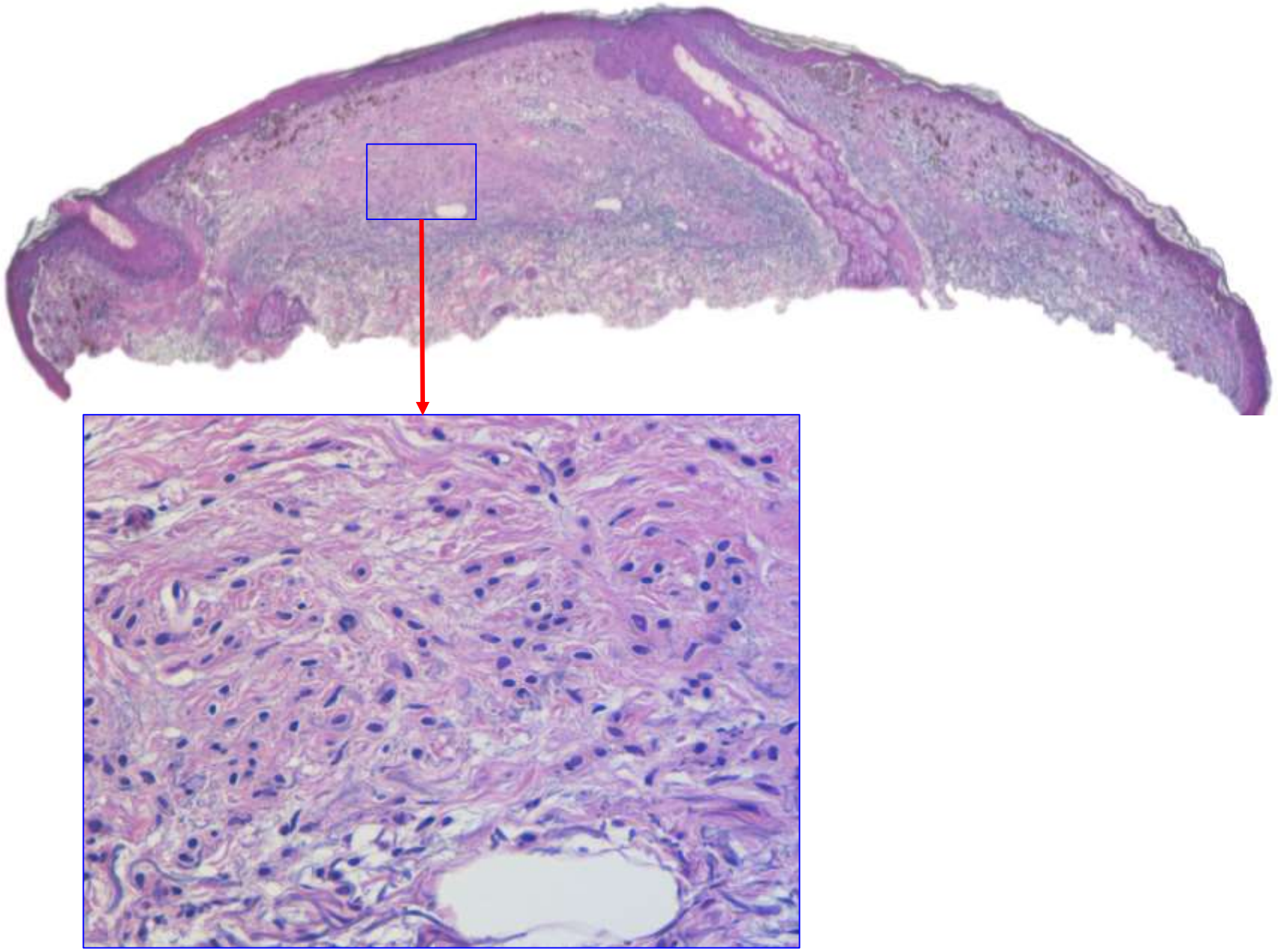
Moreover, the epidermis is hyperplastic rather than atrophic, nests predominate over solitary melanocytes, melanocytes are present in all reaches of the epidermis,

Woman, 83 y., nose

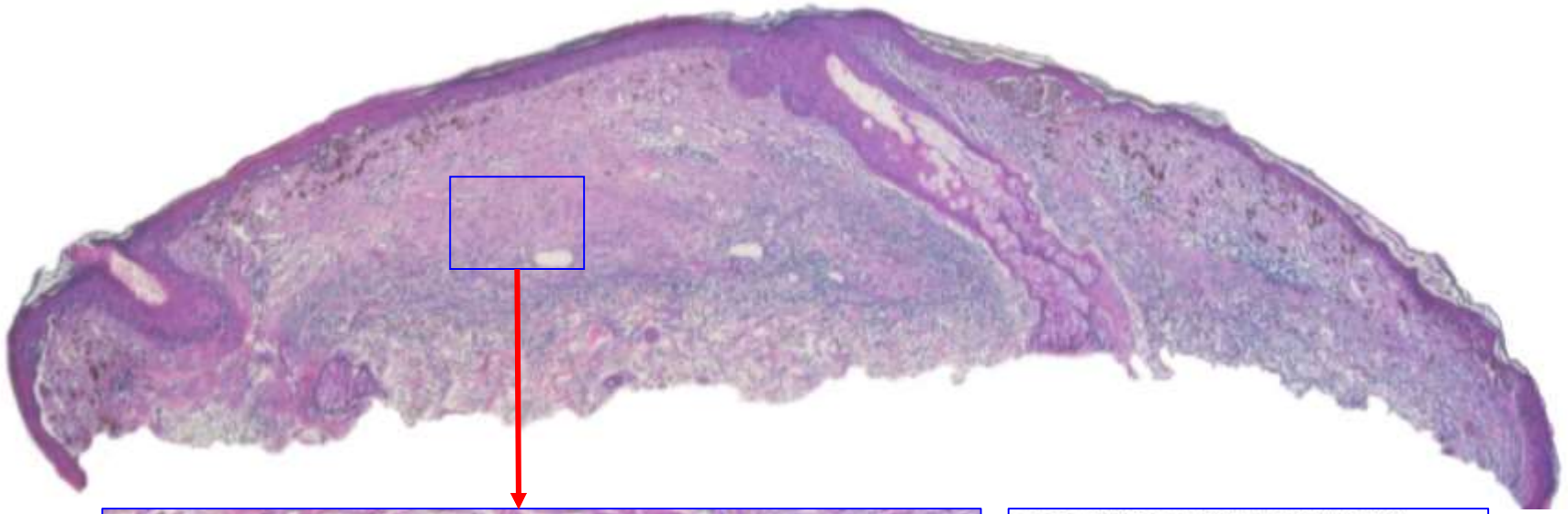
Case 10

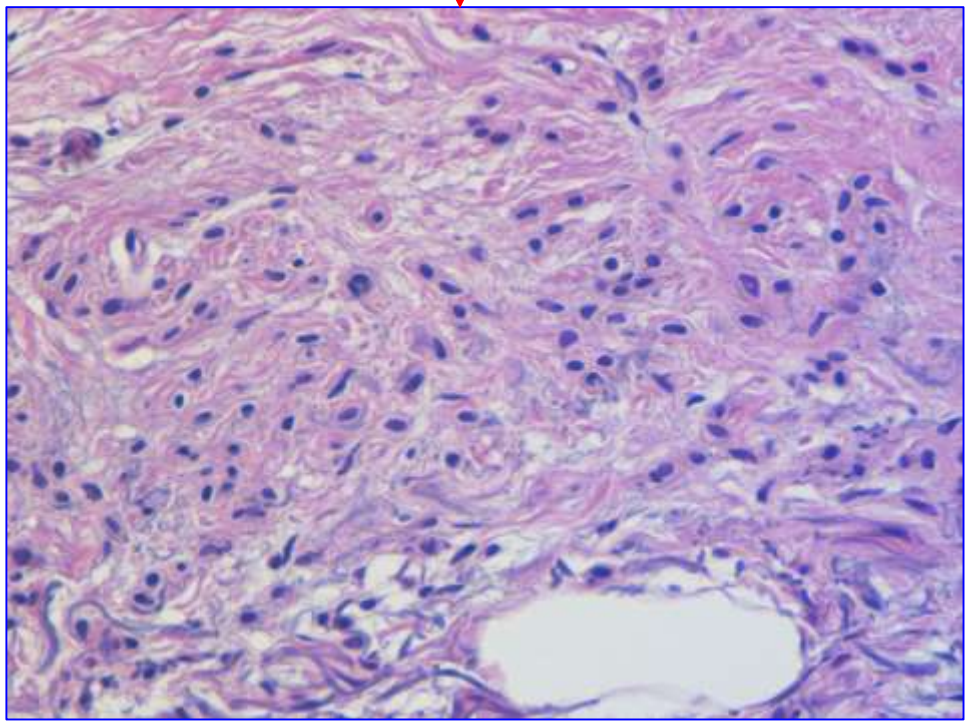


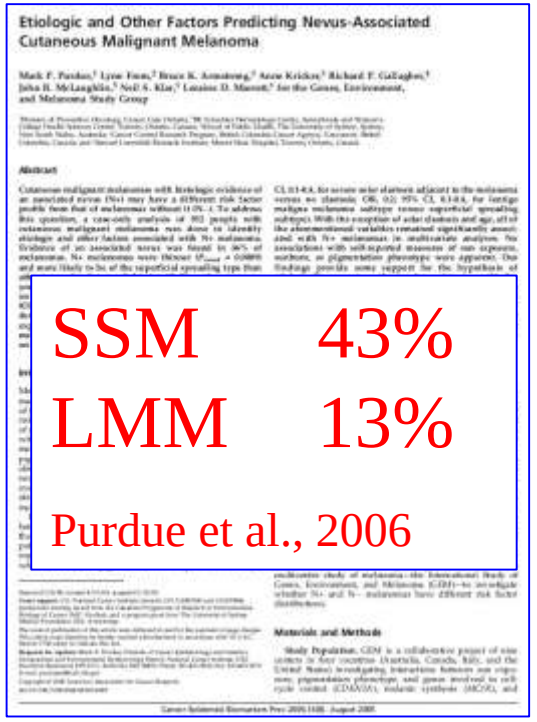
and neoplastic cells are not spindled but epithelioid. If this melanoma is classified as “lentigo maligna melanoma” because of marked solar elastosis, all other criteria must be ignored.



The same is true for the association with nevi that has been said to be rare in melanomas on sun-damaged skin. In fact, though uncommon, it is not exceptional. Of course, it may be difficult to decide whether monomorphous melanocytes in the dermis are part of the melanoma or of an associated nevus, and even if interpreted as nevus, they could be an incidental finding. After all, small nevi are also found episodically in excisional specimens of squamous or basal cell carcinoma of the head and neck.







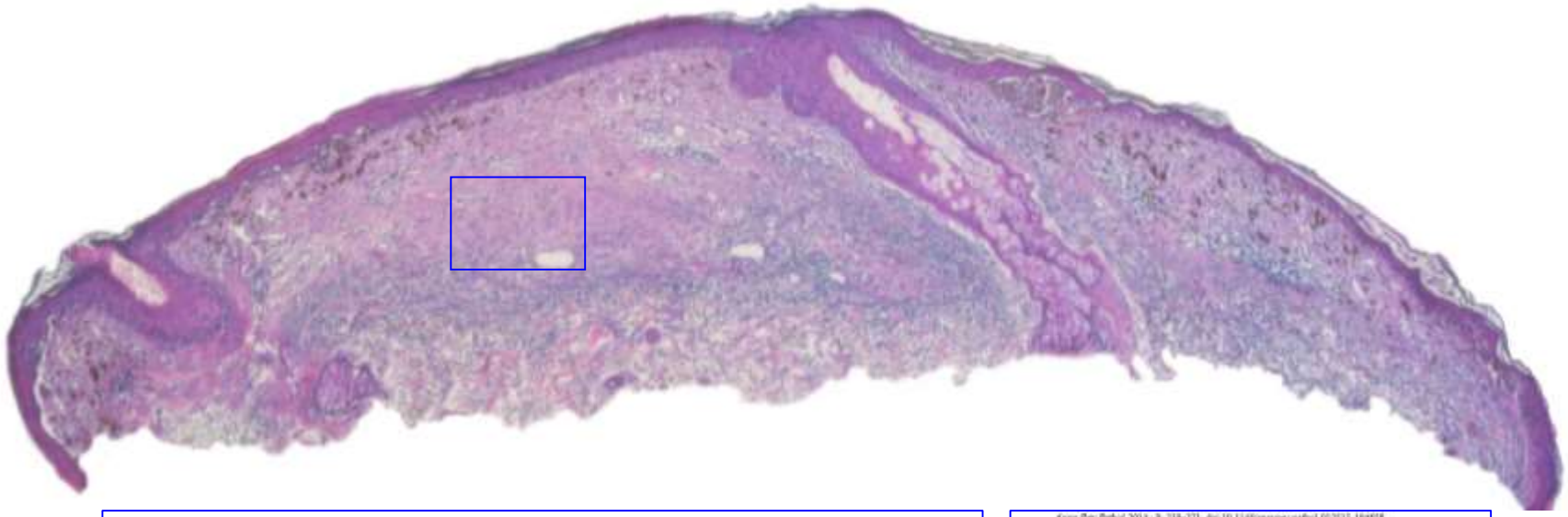
Etiologic and Other Factors Predicting Nevus-Associated Cutaneous Malignant Melanoma

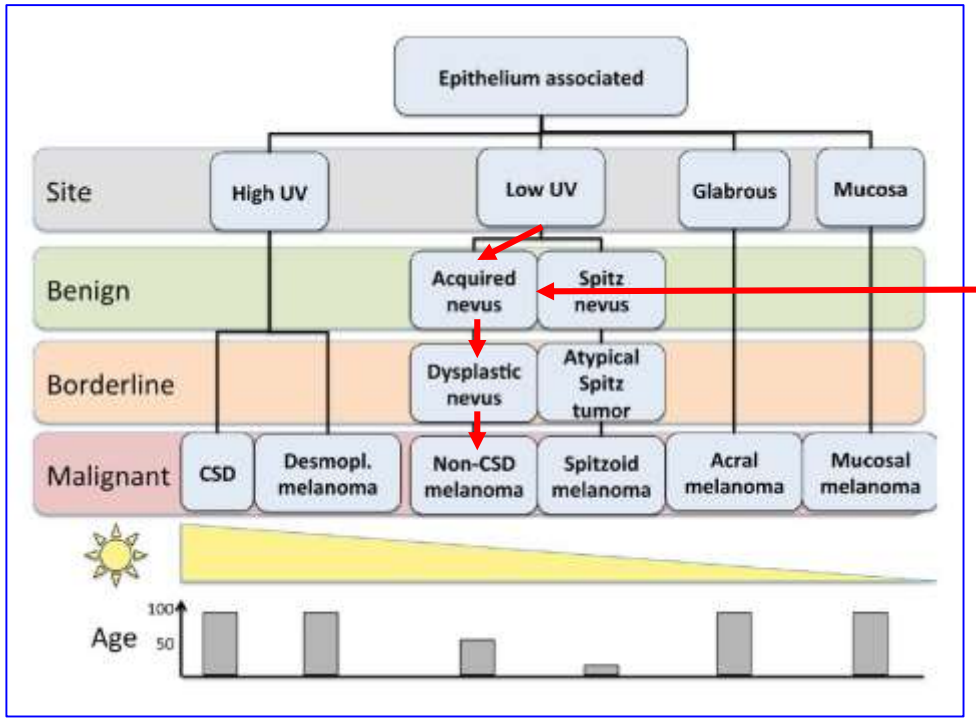
SSM 43%

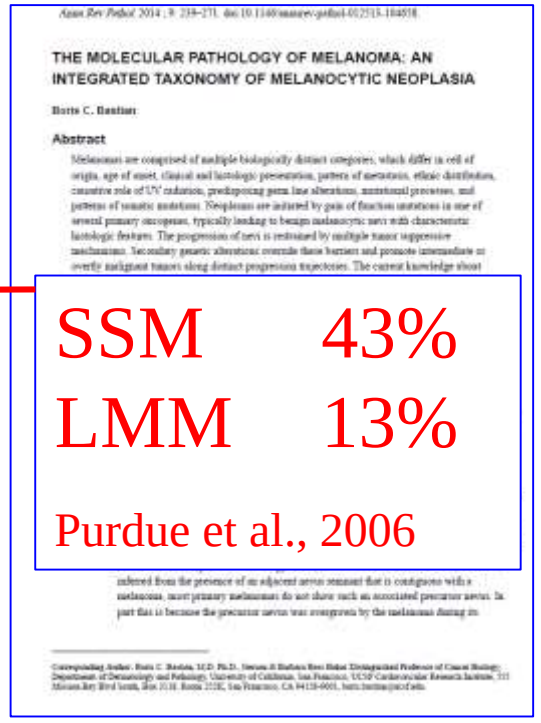
LMM 13%

Purdue et al., 2006

In the most frequently quoted study concerning “nevus-associated cutaneous malignant melanoma,” an associated was found in 43% of superficial spreading and in 13% of lentigo maligna melanomas. To use these numbers to infer







THE MOLECULAR PATHOLOGY OF MELANOMA: AN INTEGRATED TAXONOMY OF MELANOCYTIC NEOPLASIA

Boris C. Bastian

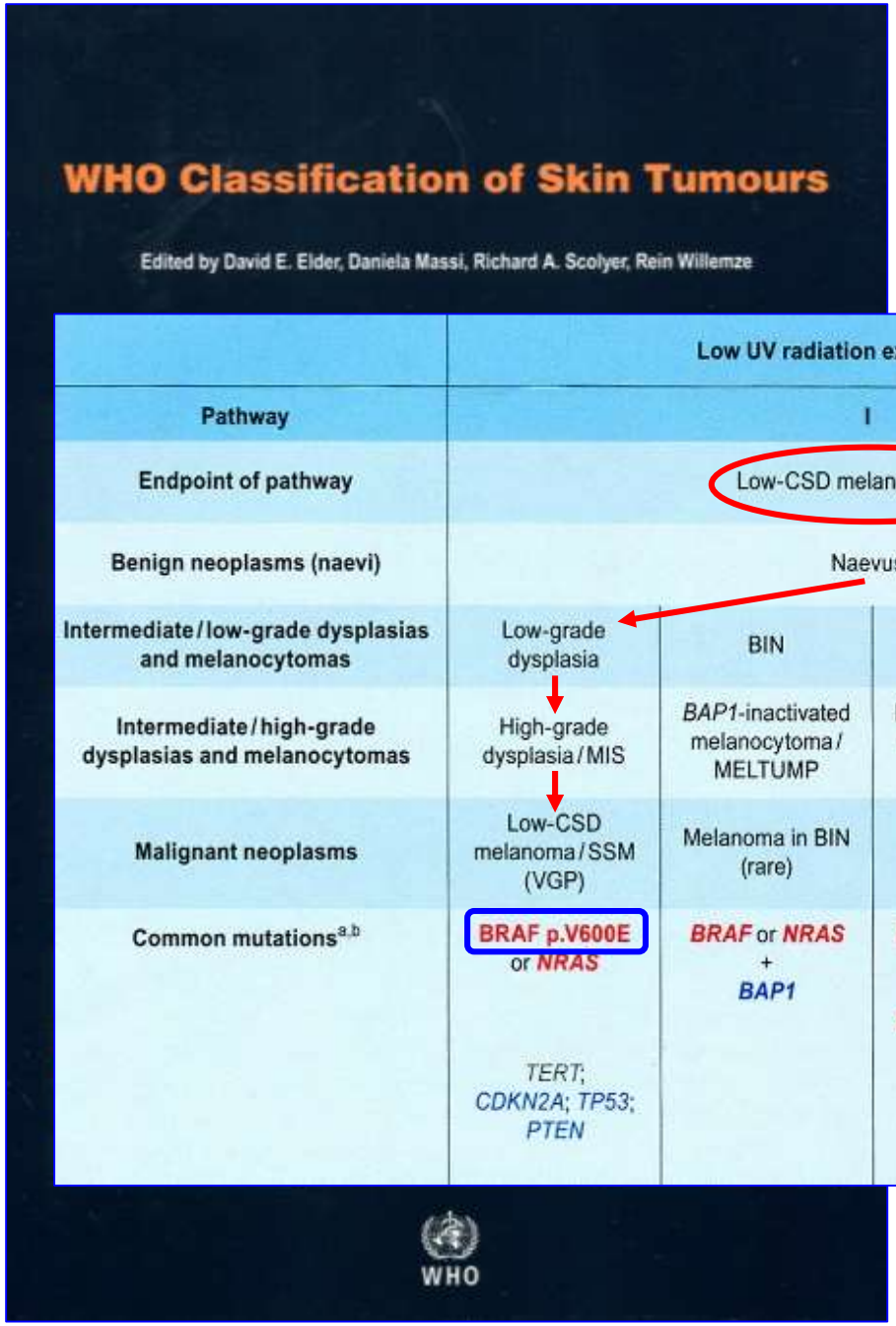
Abstract

SSM 43%

LMM 13%

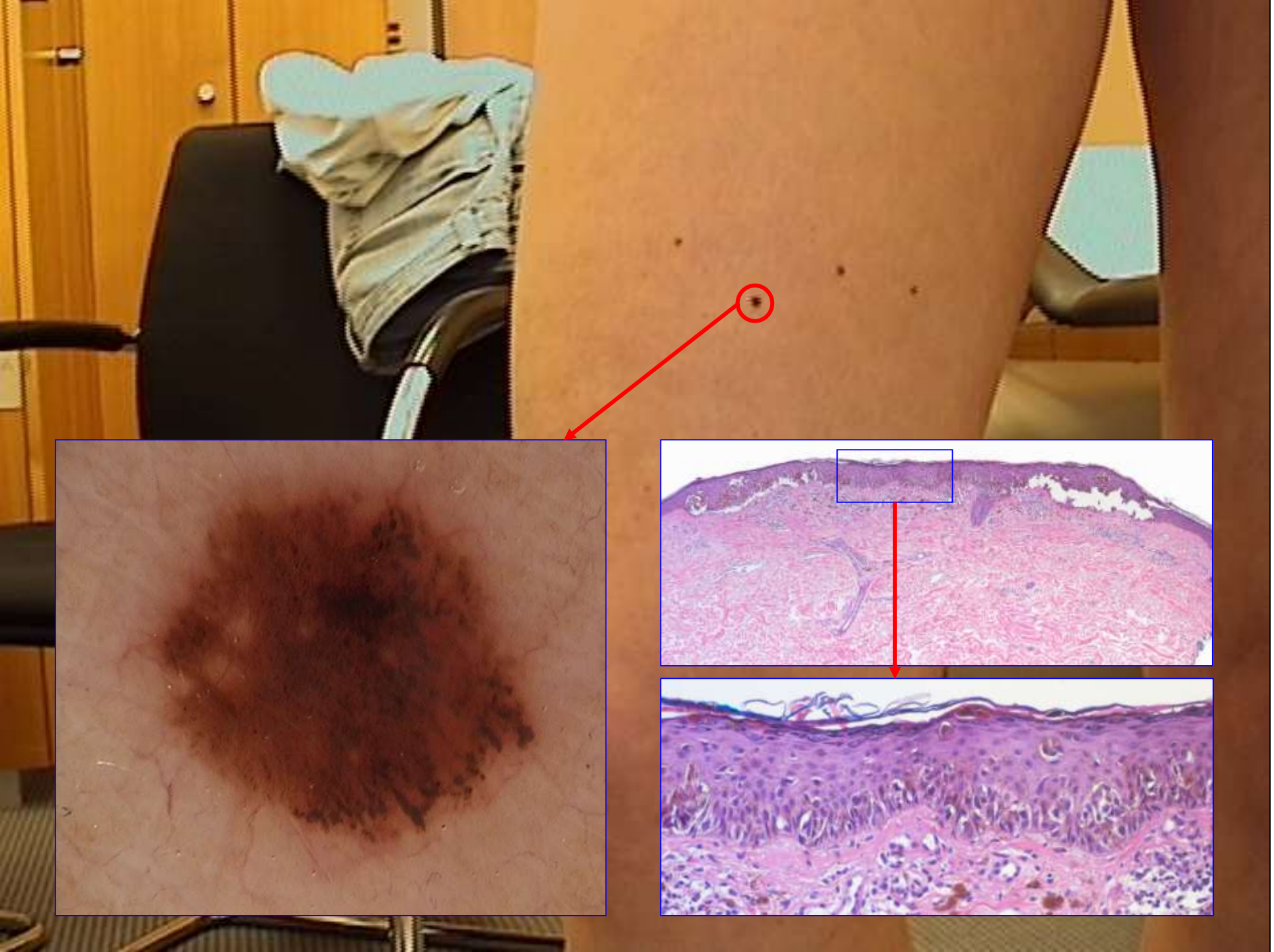
Purdue et al., 2006

that there are fundamental biologic differences between melanomas in skin with high and low UV irradiation and that the latter principally arise from a pre-existing nevus, as has been done in this article about the taxonomy of melanoma by Boris Bastian, is more than gutsy.

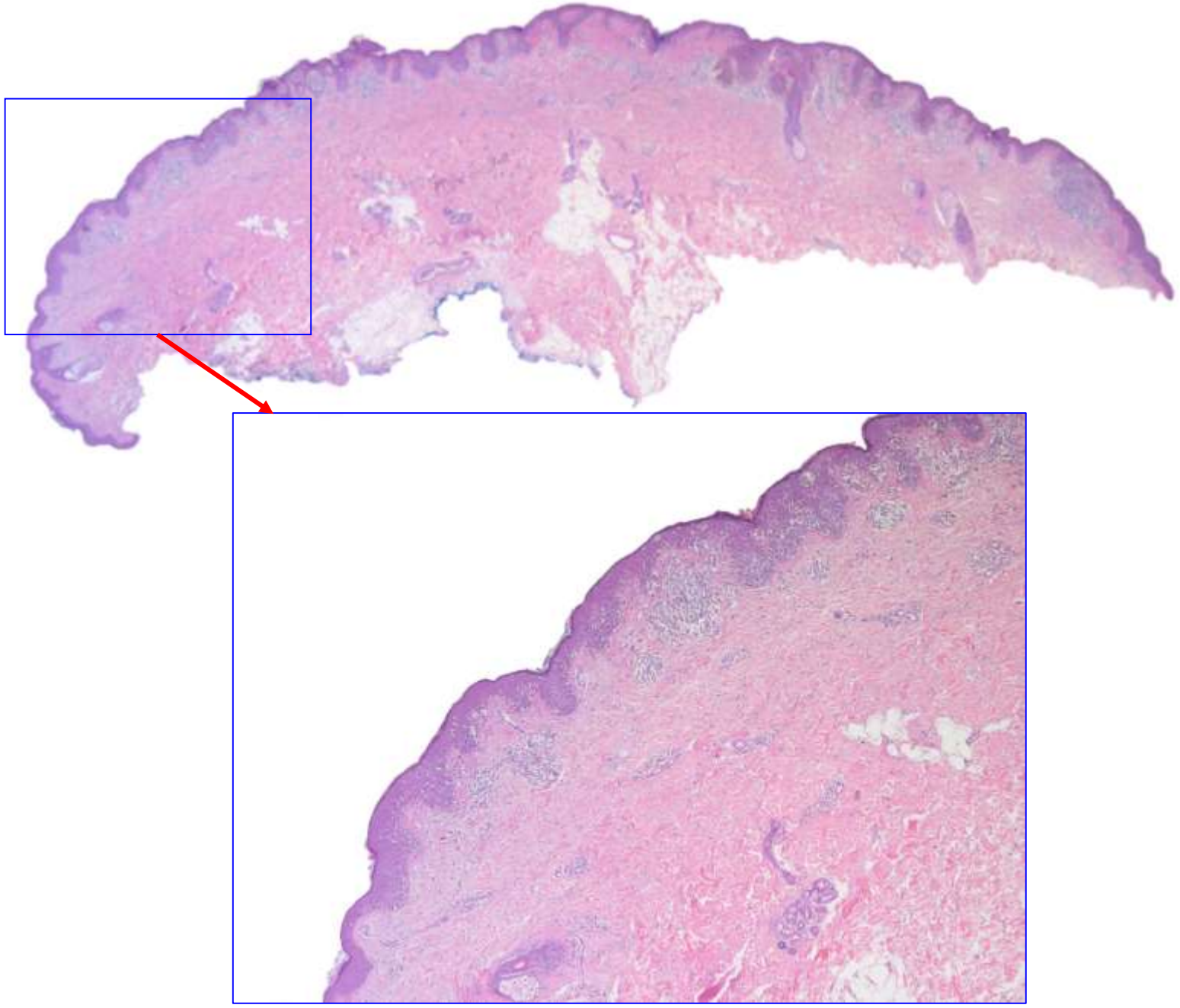


	Low UV radiation exposure / CSD				High UV radiation exposure / CSD	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma / SSM				High-CSD melanoma / LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate / low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate / high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS	*BAP1*-inactivated melanocytoma / MELTUMP	Deep penetrating melanocytoma / MELTUMP	PEM / MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma / SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	***BRAF* p.V600E** or ***NRAS*** *TERT*; *CDKN2A*; *TP53*; *PTEN*	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS***; ***BRAF* (non-p.V600E)**; ***KIT***; or *NF1* *TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET* *TERT*; *NFKBIE*; *NRAS*; *PIK3CA*; *PTPN11*

Nonetheless, this hypothesis has found entrance into the new WHO classification of melanoma. The chief reason for it is the fact that not only most melanomas in episodically UV-exposed skin but also most nevi harbor BRAF mutations. It seems that the V600E mutation in the BRAF gene is a first step in the development of nevi and melanomas, but one should not confuse the molecular basis with the emerging lesion.

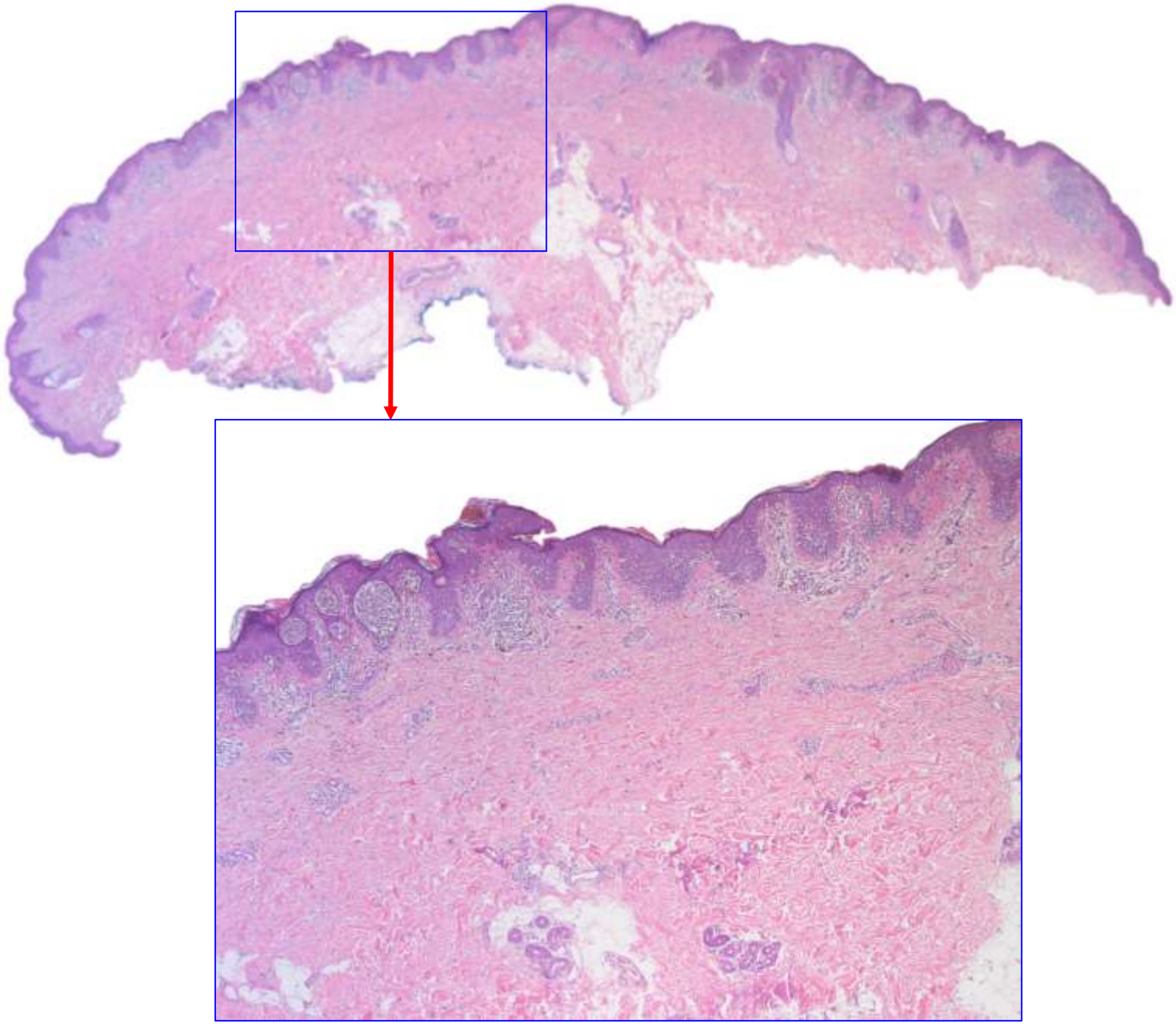


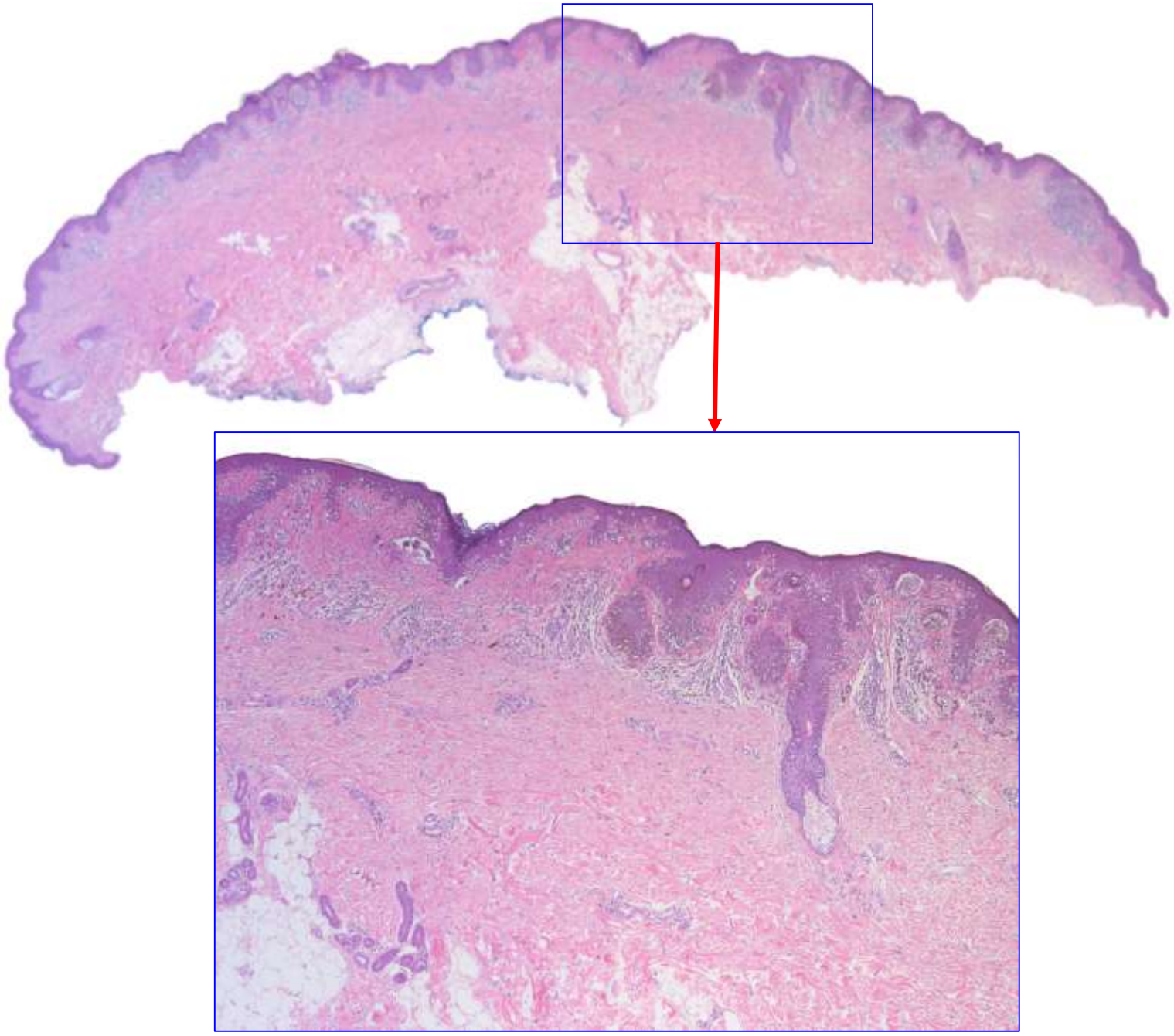
A nevus is not a mutation but a tumor, and that tumor cannot be demonstrated in the vast majority of melanomas. From the outset, melanomas behave differently from nevi and can be recognized as being malignant early-on. By that time, the decisive phase of carcinogenesis must have happened.



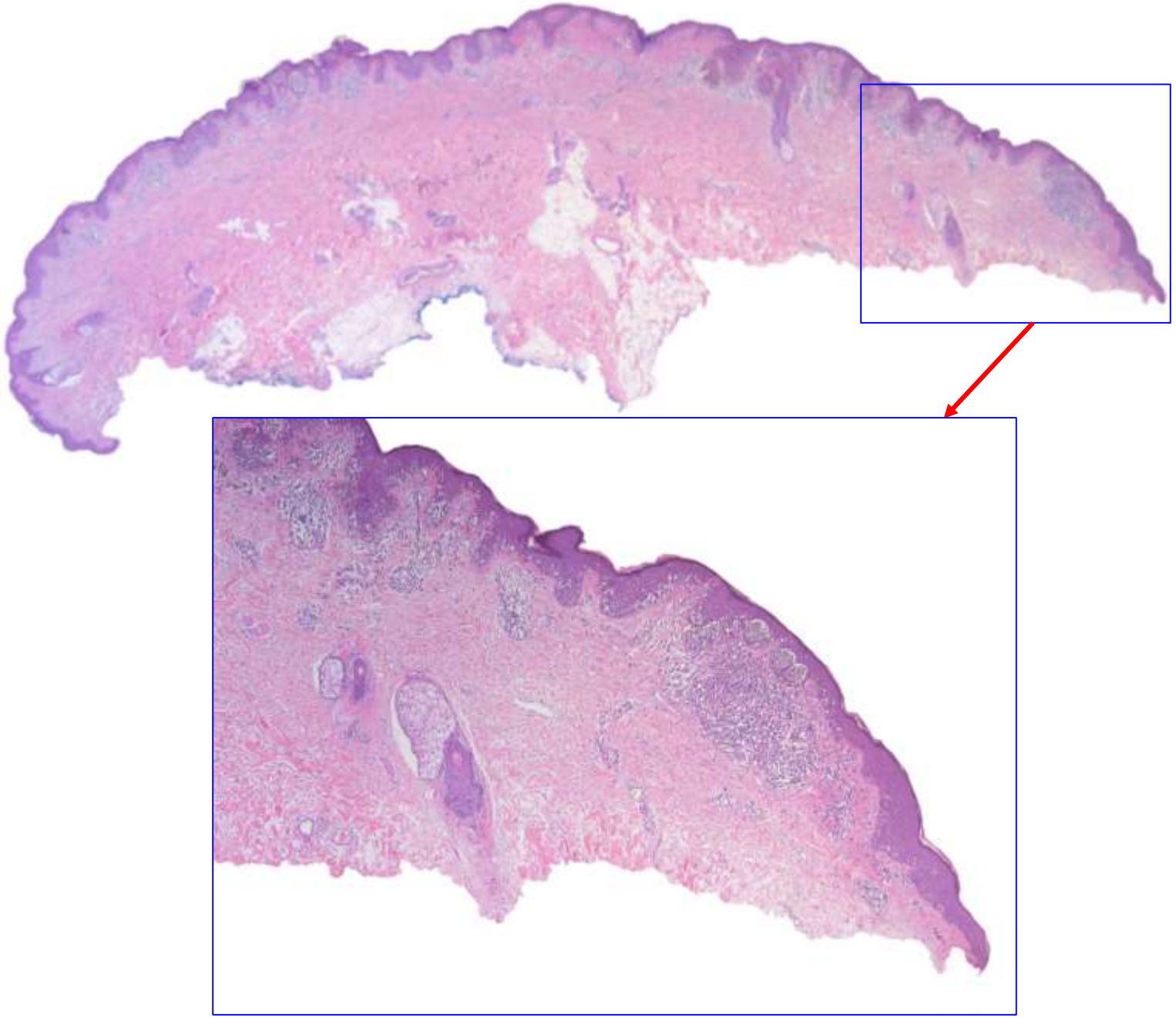
Then they enlarge, and the irregularity of growth as a direct reflection of their biologic behavior in the tissue becomes more apparent, but wherever one looks,

there are the same cells,
one clonal proliferation,

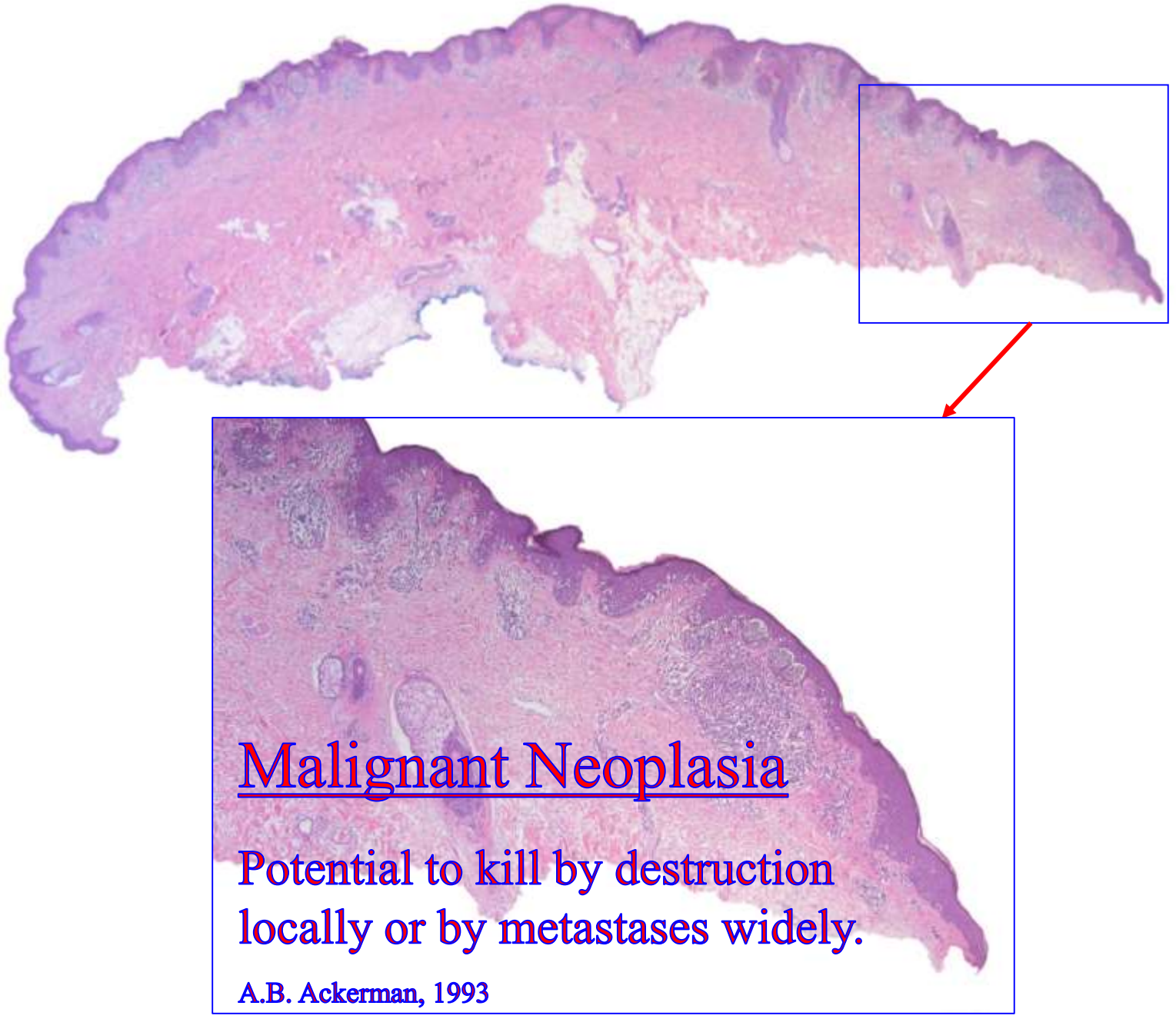




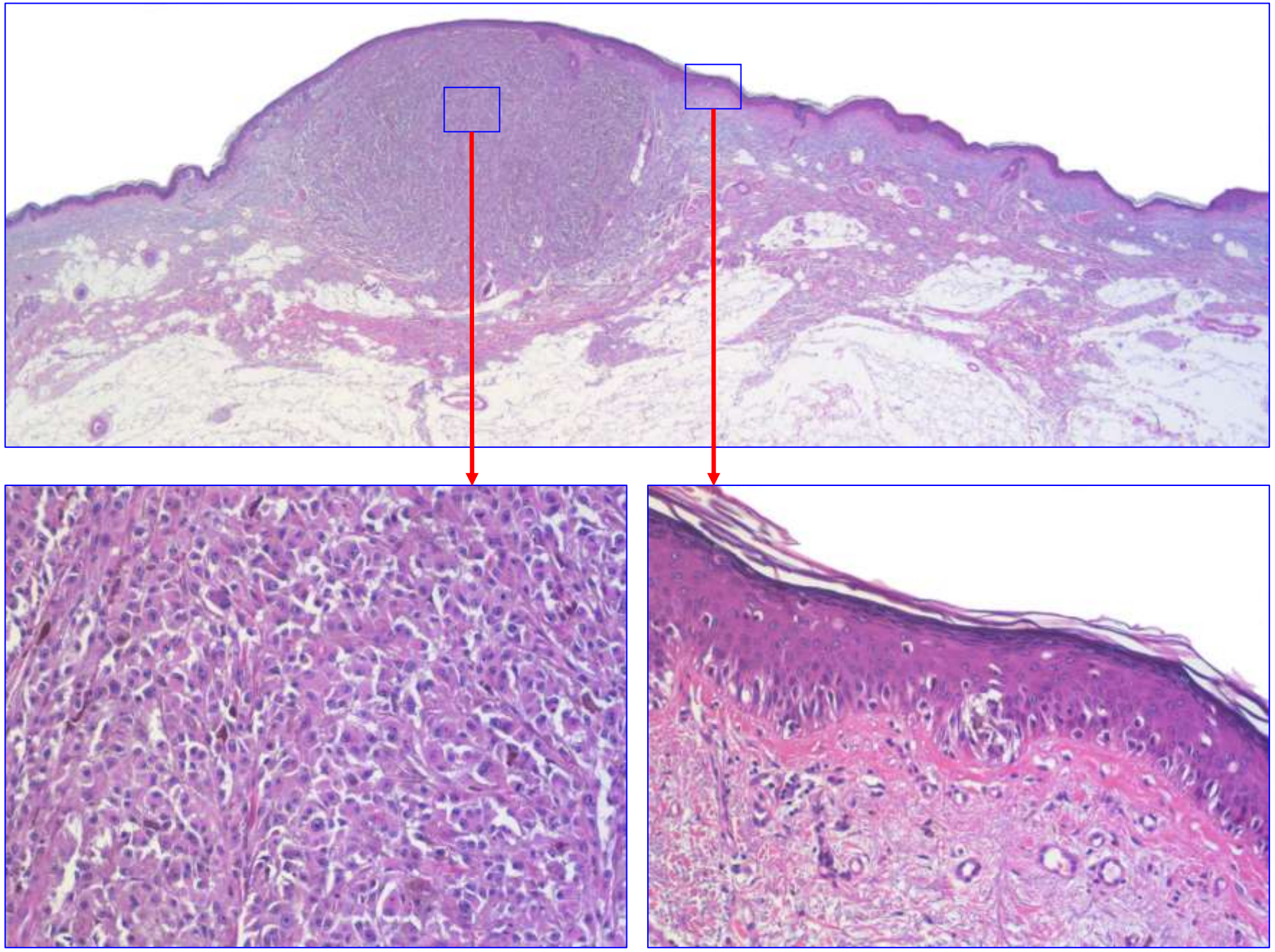
one and the same
pathologic process



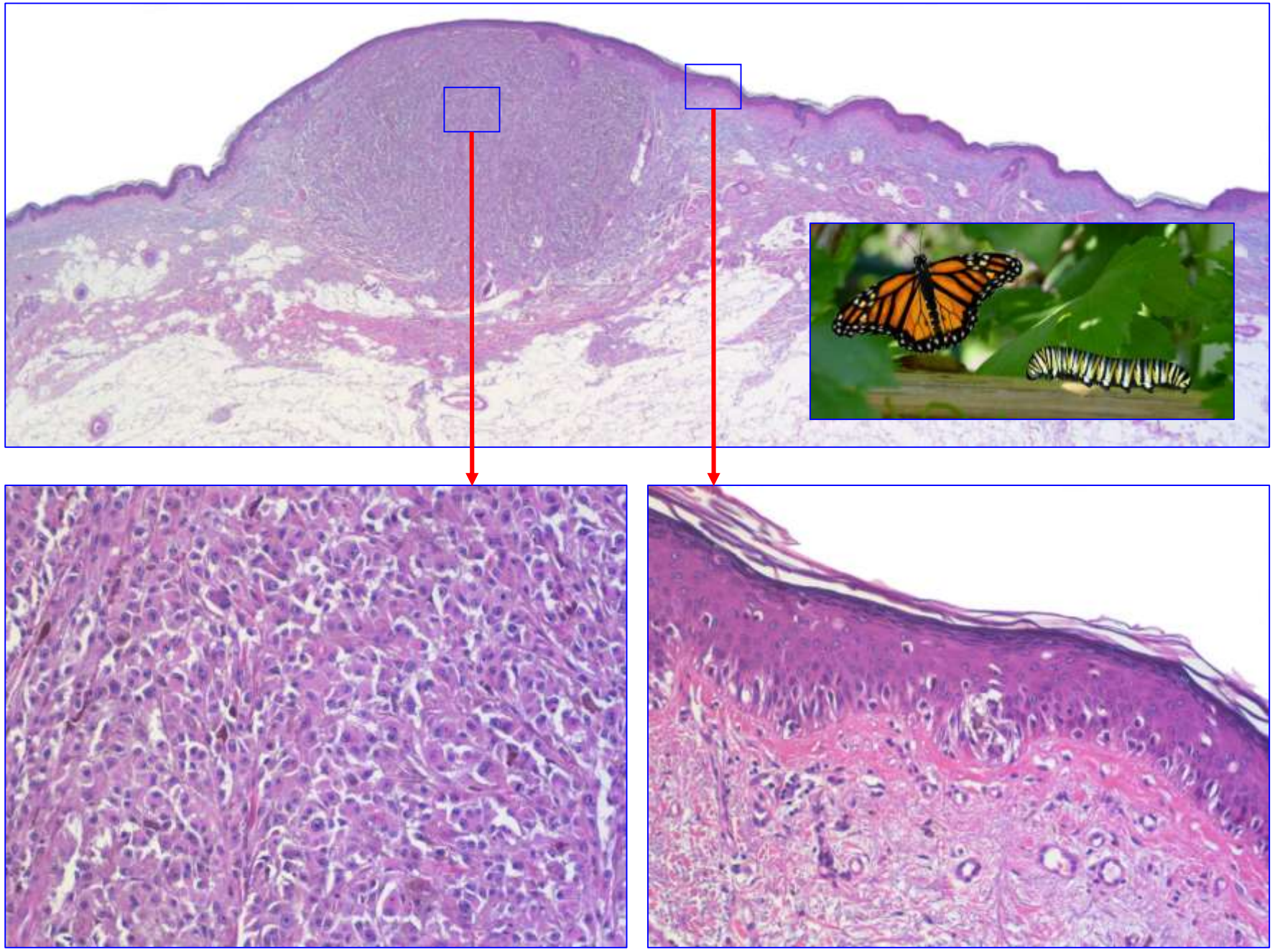
that fulfills the definition of malignant neoplasia, namely,



the *"potential to kill by destruction locally or by metastases widely."*
If one does not interfere, this melanoma will continue to grow,



and additional mutations lead to the development of new populations of cells. In other words, growth is associated not only with quantitative but also qualitative changes. But this is true for all phenomena in nature,



and often qualitative changes are far more striking. They do not suffice to postulate a new biologic entity.

Follow-up of melanocytic skin lesions with digital epiluminescence microscopy: Patterns of modifications observed in early melanoma, atypical nevi, and common nevi

Harold Kittler, MD,[a] Hubert Pehamberger,
and Michael Binder, MD[a] W

Background: Digital epiluminescence microscopy (DELM)
the follow-up of melanocytic nevi. One of the promises of t
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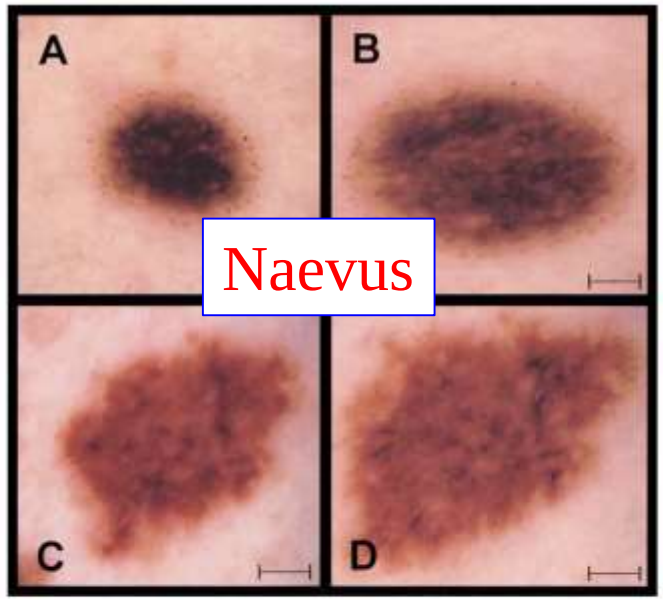
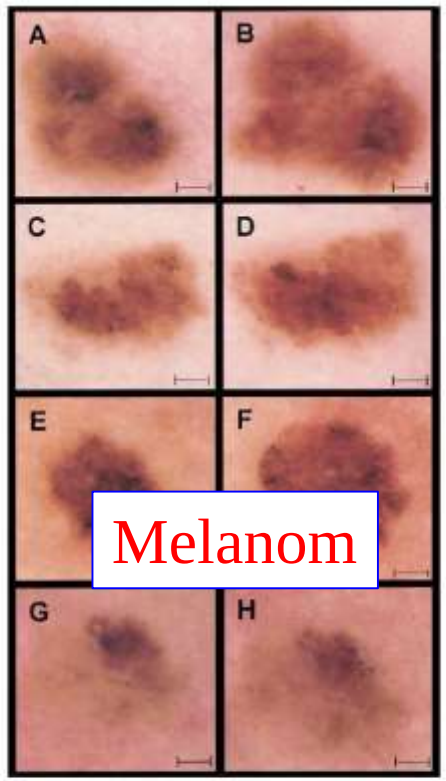
of morphologic modifications typical for early melanoma. DELM may therefore serve as a useful tool to improve the surveillance of patients with multiple atypical nevi. (J Am Acad Dermatol 2000;43:467-76.)



Naevus

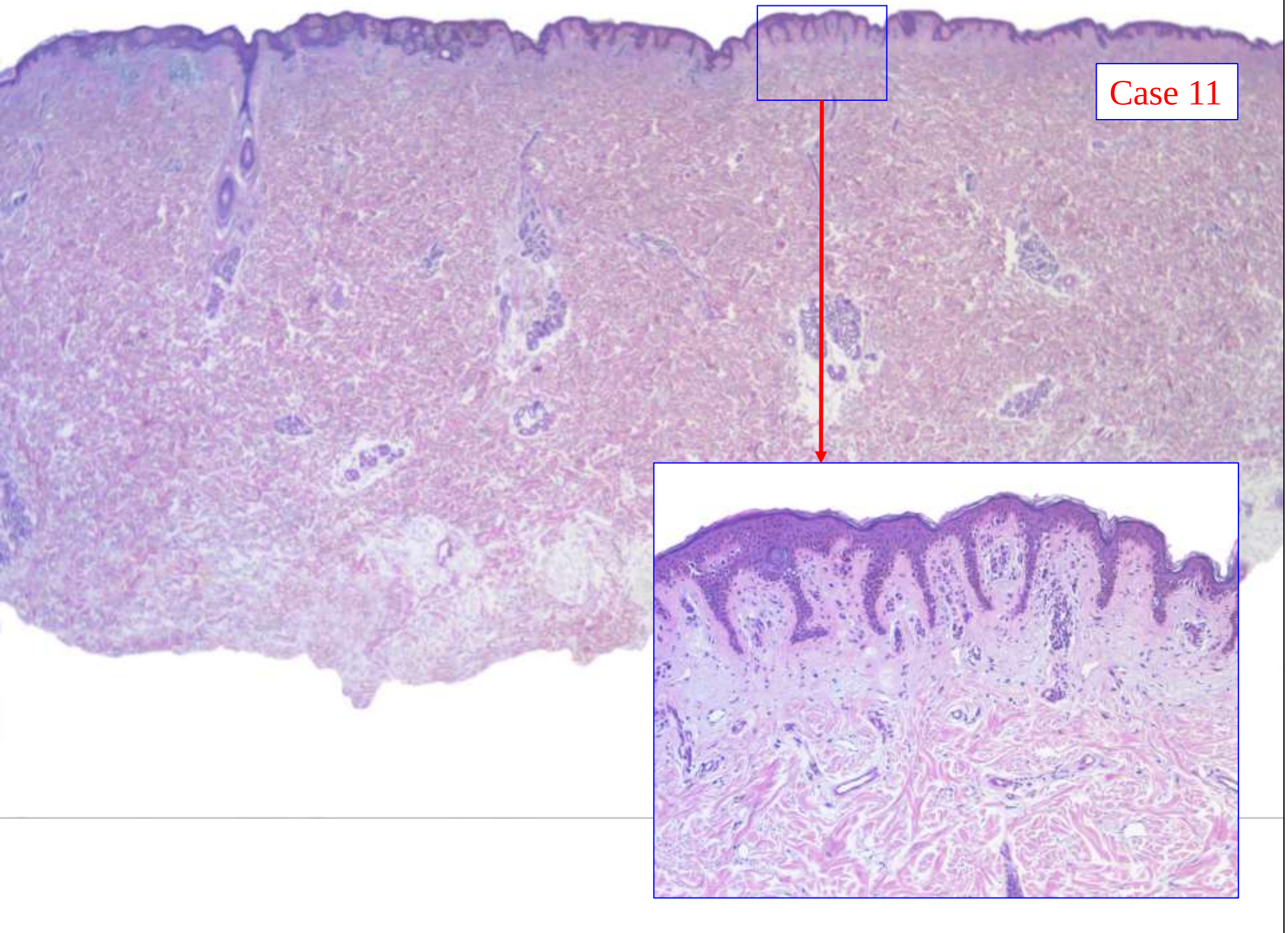
Fig 1. DELM images of two benign melanocytic skin lesions. **A** and **B**, Common nevus with symmetric enlargement without substantial structural modifications. *Right image* **(B)** was obtained 6 months after *left image*. Peripheral rim of brown globules **(A)** is a highly characteristic feature of symmetrically enlarging common nevi. **C** and **D**, Atypical nevus with symmetric enlargement. Substantial structural modifications are not observed. This lesion can also be identified on the photographic overview of the patient shown in Fig 5 *(white arrow)*. All magnifications are identical. *Bar* = 1 mm.



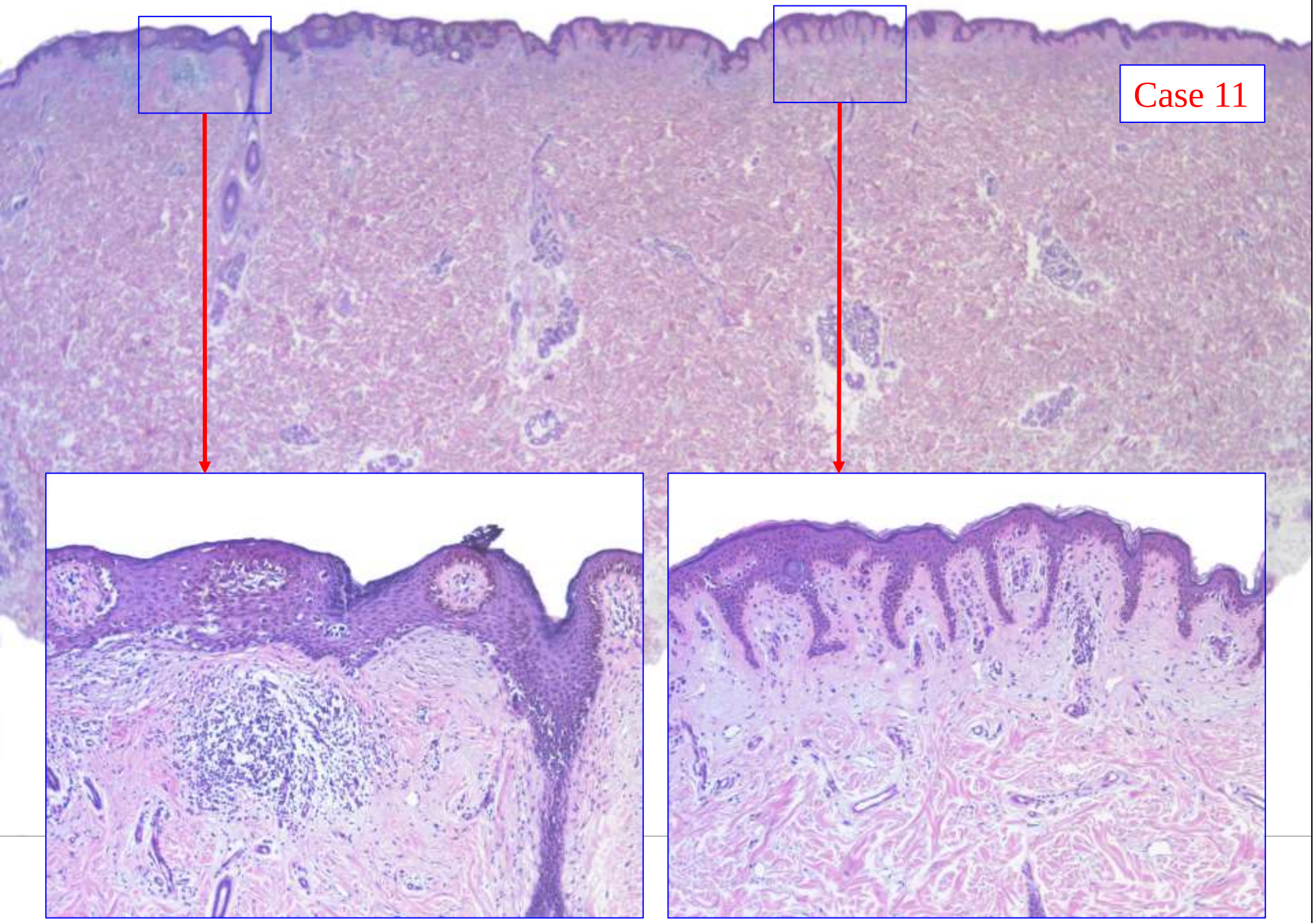
Melanom

Fig 4. Four early melanomas with substantial morphologic modifications over time identified by follow-up with DELM. **A** and **B**, Superficial spreading melanoma (Breslow thickness, 0.55 mm; Clark level, II). **B**, This image was obtained 14 months after image shown in **A**. Melanoma shows focal enlargement associated with a change in shape. **C** and **D**, Superficial spreading melanoma in situ. **D**, This image was obtained 7 months after image shown in **C**. This melanoma shows multifocal nonsymmetric enlargement and a change in the prominent and irregular pigment network (it appeared in areas where it had not been present previously or regressed where previously present). **E** and **F**, Superficial spreading melanoma (Breslow thickness, 0.3 mm; Clark level, II). This melanoma also shows multifocal nonsymmetric enlargement associated with a change in shape as well as the appearance of a highly irregular and prominent pigment network. **F**, This image was obtained 11 months after image shown in **E**. **G** and **H**, Superficial spreading melanoma in situ. **H**, This image was obtained 7 months after image shown in **G**. This melanoma did not enlarge but showed focal appearance of black dots in irregular distribution with varying size. All magnifications are identical. *Bar* = 1 mm.

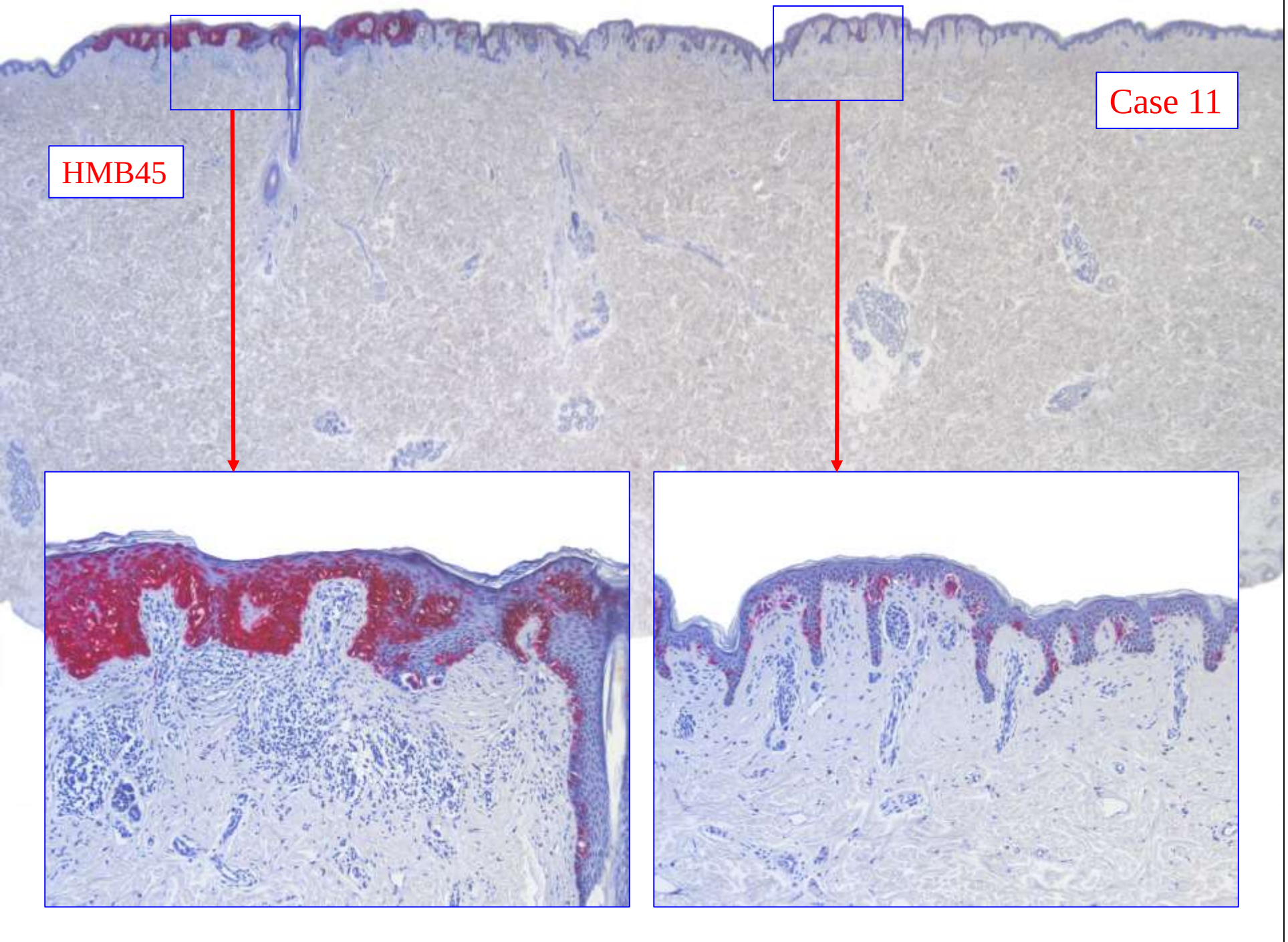
A melanocytic neoplasm without the potential to kill, i.e., a melanocytic nevus, displays a completely different behaviour from its outset, as has been demonstrated conclusively by dermatoscopic follow-up studies years ago. Morphologically, it has a more regular architecture that usually allows for its specific recognition.



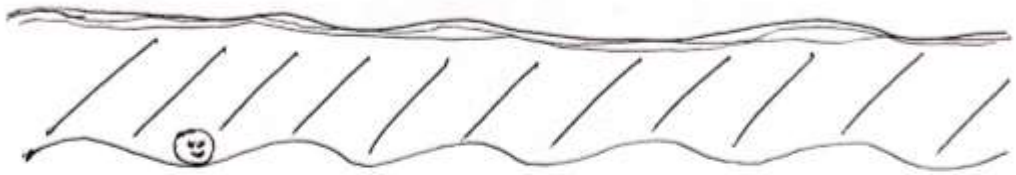
From such a nevus, a melanoma may arise, characterized by a different population of cells

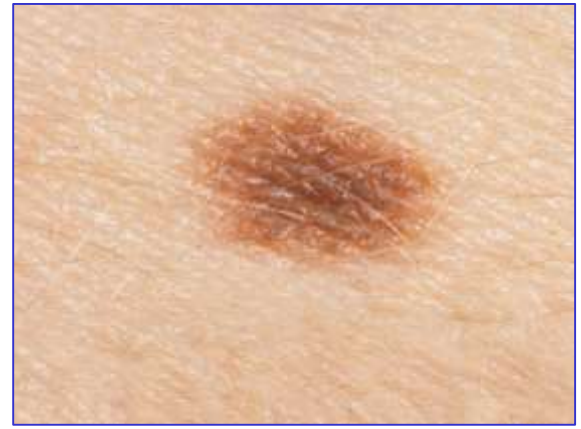


that also show a different pattern of proliferation, as illustrated by case 11 of the self assessment. Data concerning the prevalence of that event vary markedly in the literature, but there is unanimity that it is very rare.

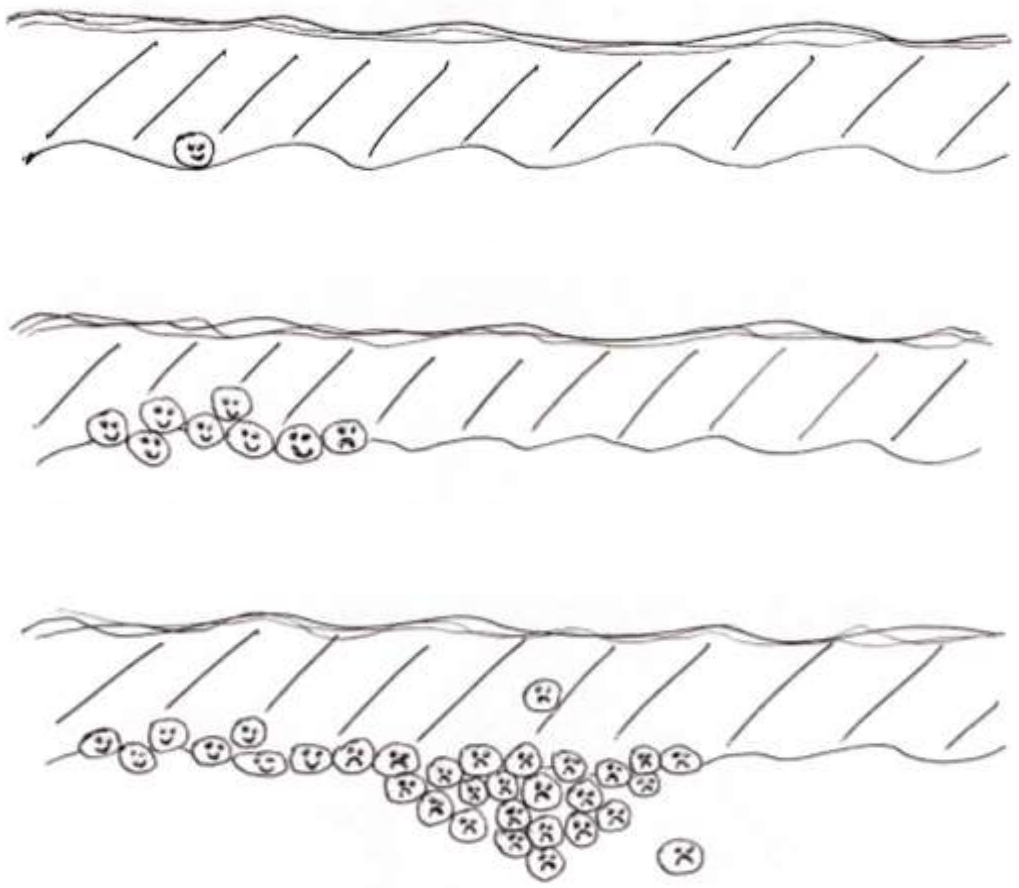


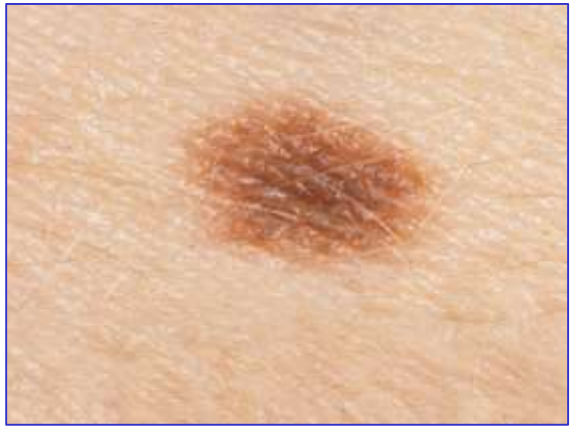
Different parts of the lesion are not always as sharply demarcated from one another as in case 11, but they always result from a clonal proliferation.

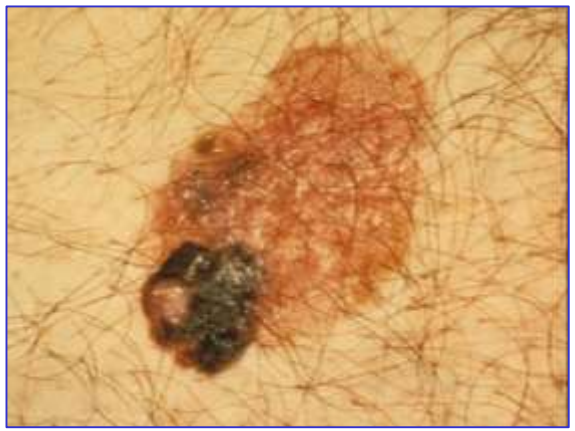




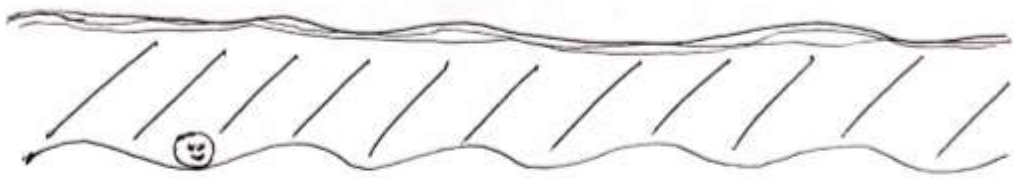
One cell of an originally benign lesion becomes bad and starts to proliferate, a melanoma arises on a nevus. This may happen.

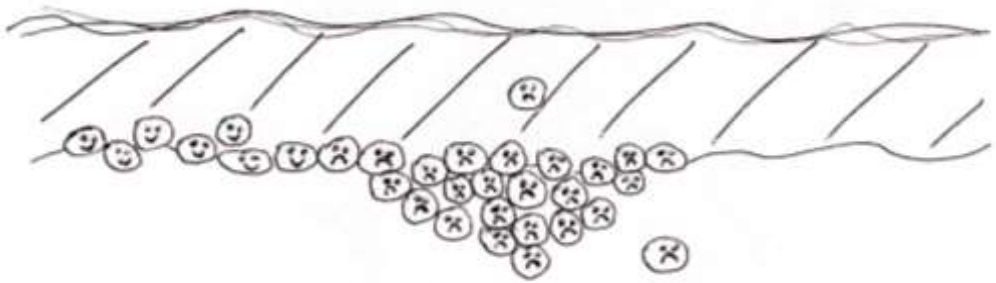


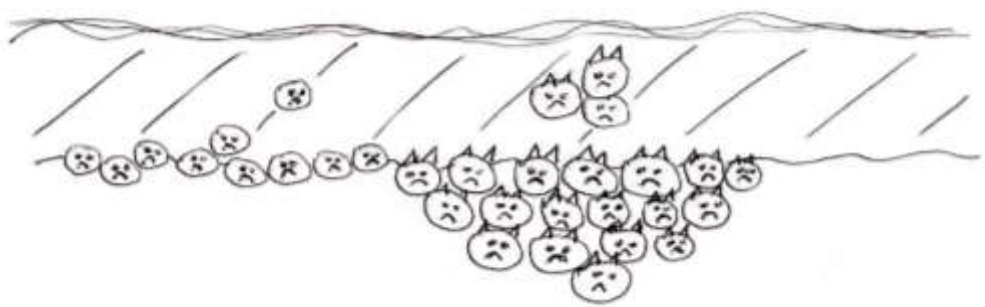


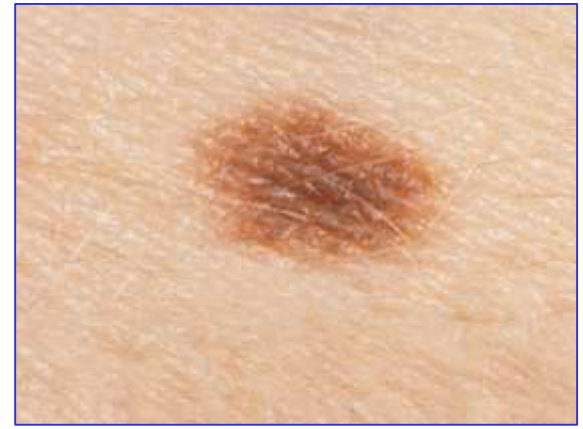


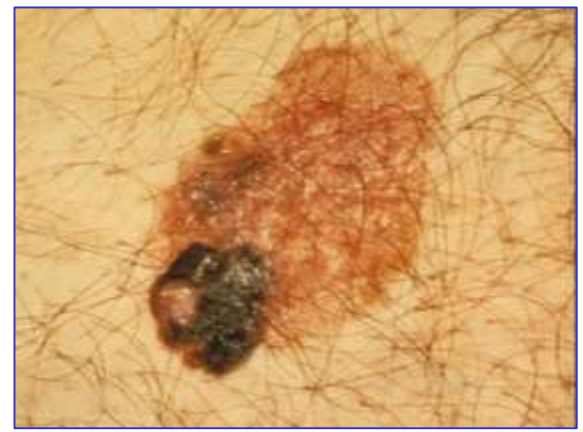
a melanoma arises on a nevus. This may happen.

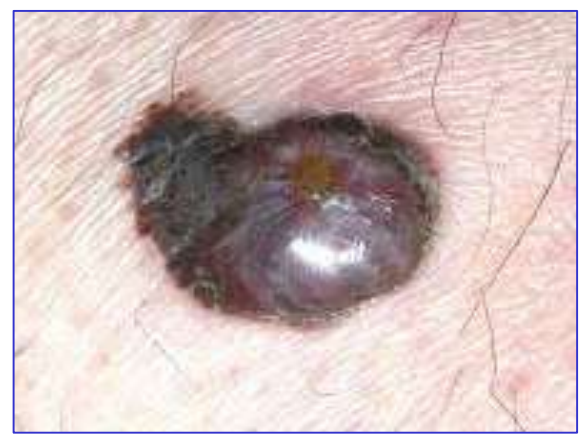




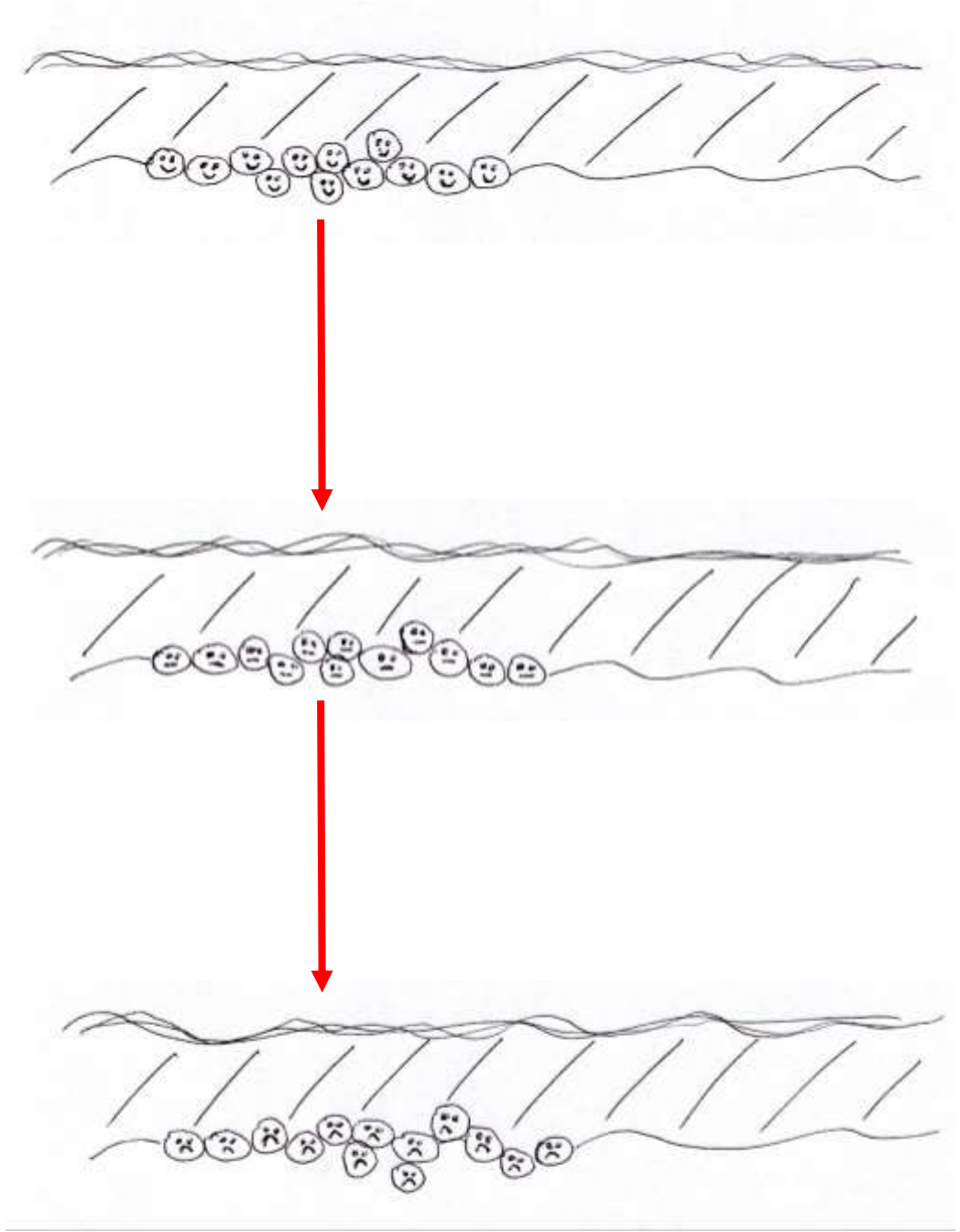


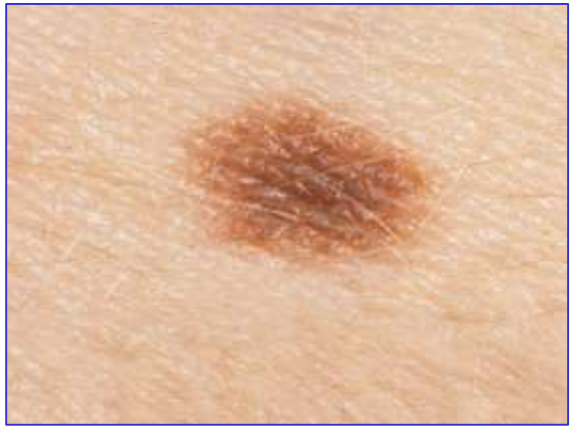


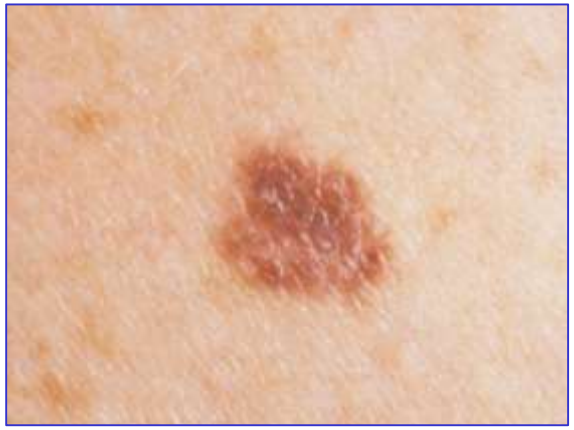


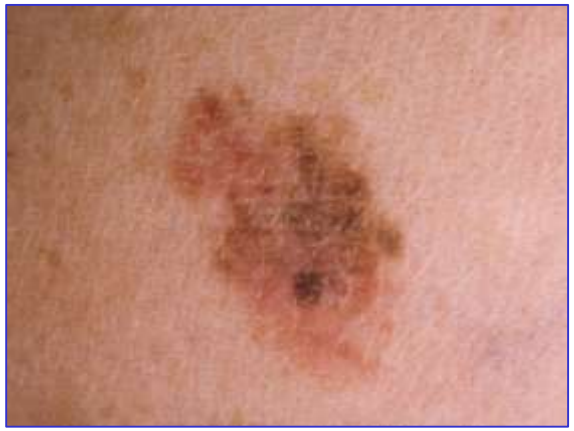


Within the growing melanoma, new clones of cells may arise that turn from bad to truly diabolical. This is common in advanced melanomas.

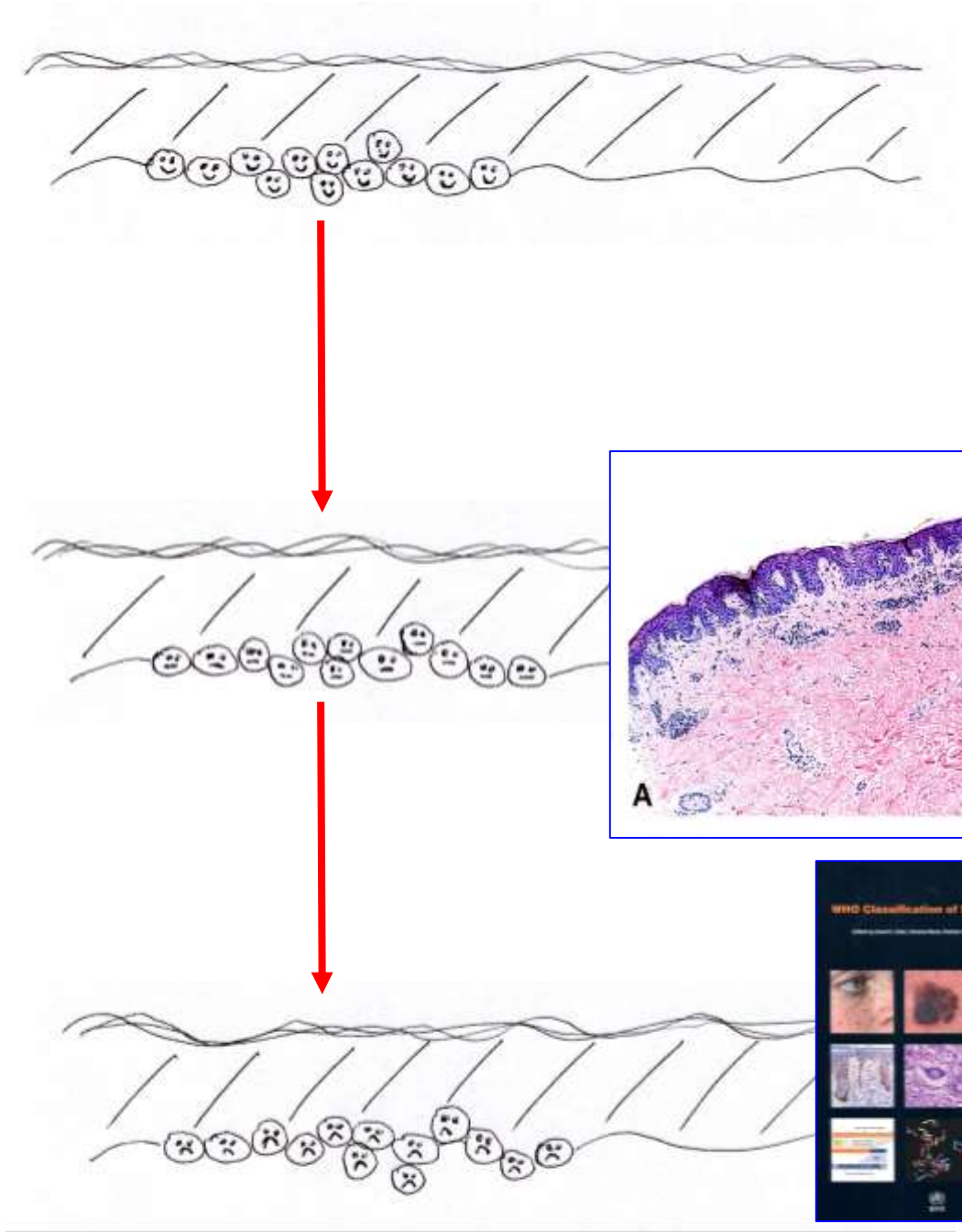


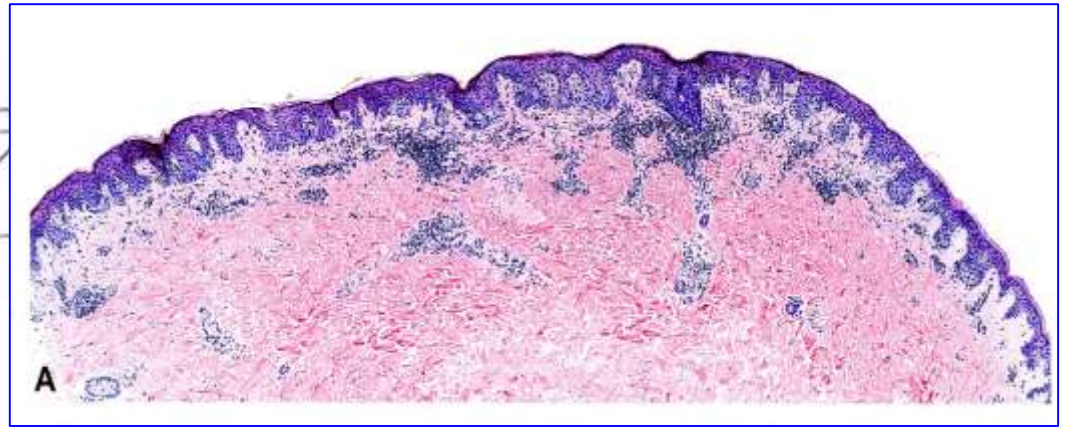






But what never happens is a gradual change in the character of all neoplastic, turning, in synchrony, from being friendly and benign to being somewhat disgruntled, and really bad in the end. This is pure fiction,



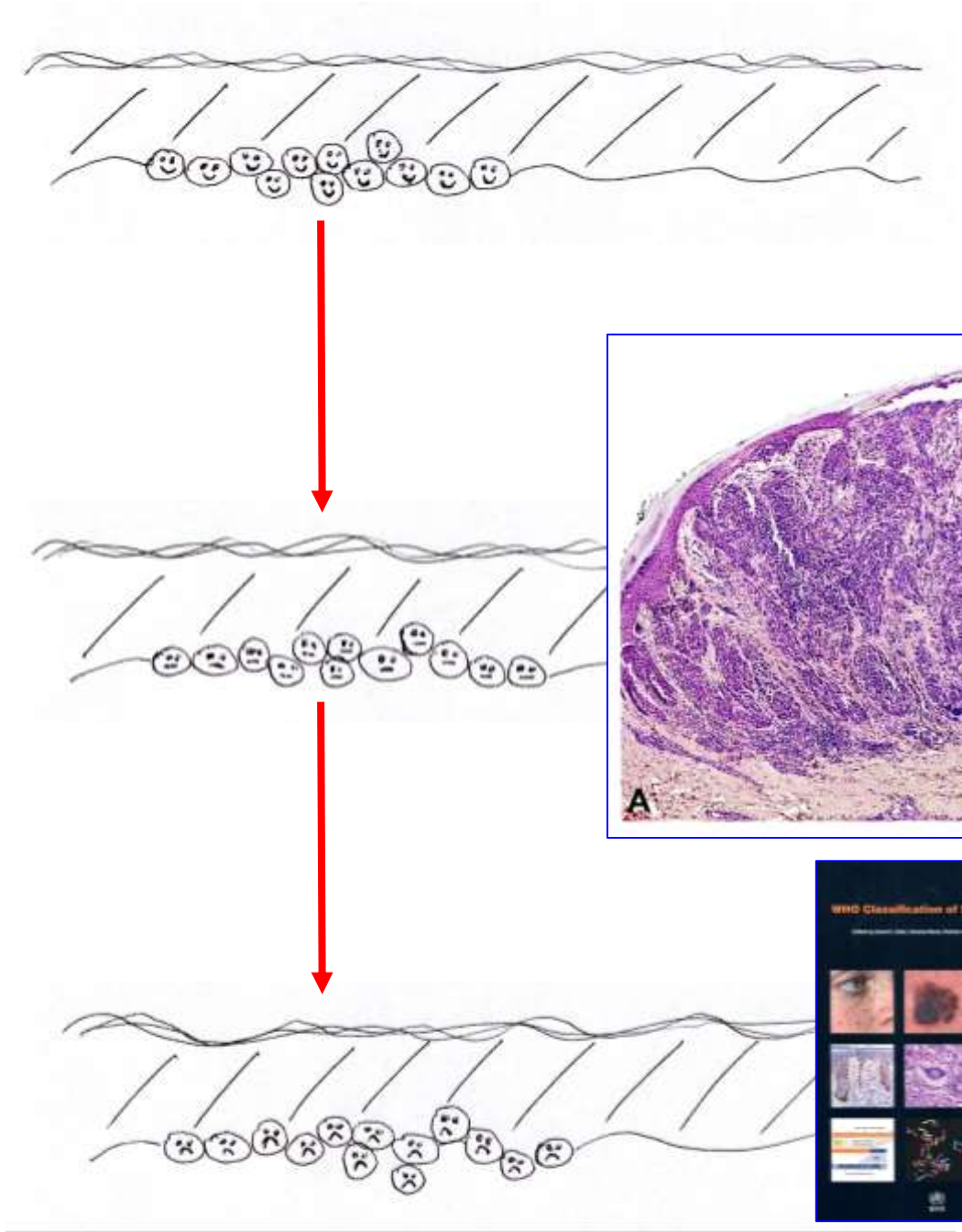


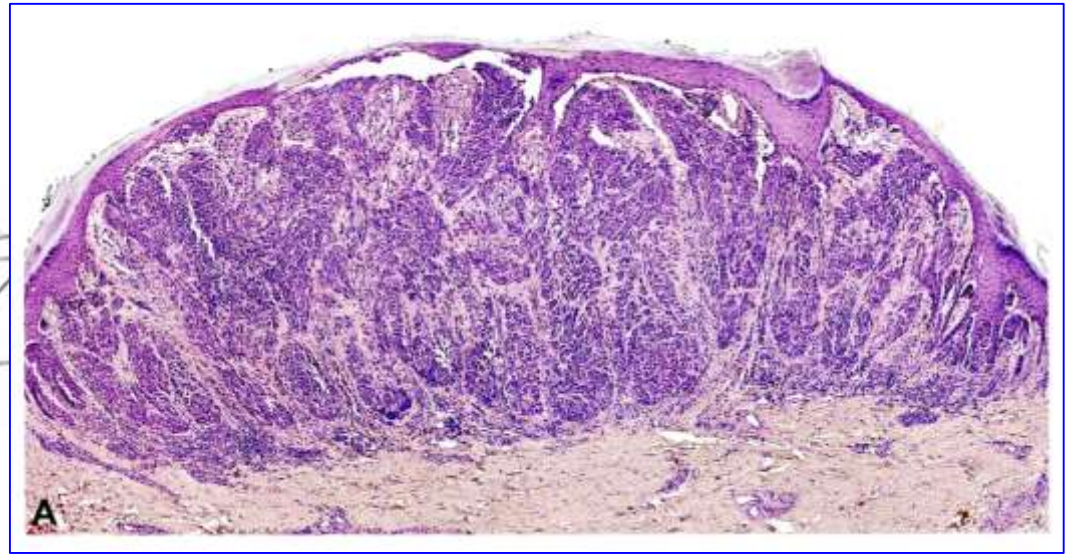
WHO:

Intermediate lesion

„Compound dysplastic nevus, high grade“

but that fiction is conveyed in the WHO classification. This lesion is said to be a “compound dysplastic-nevus, high grade,” by definition a so-called “intermediate lesion.” In actuality, it is a completely banal Clark’s nevus with a regular architecture, evenly distributed cells, and the same type of cells from left to right; there is no evidence of a new, aggressive cell population on top of a benign one.





WHO:

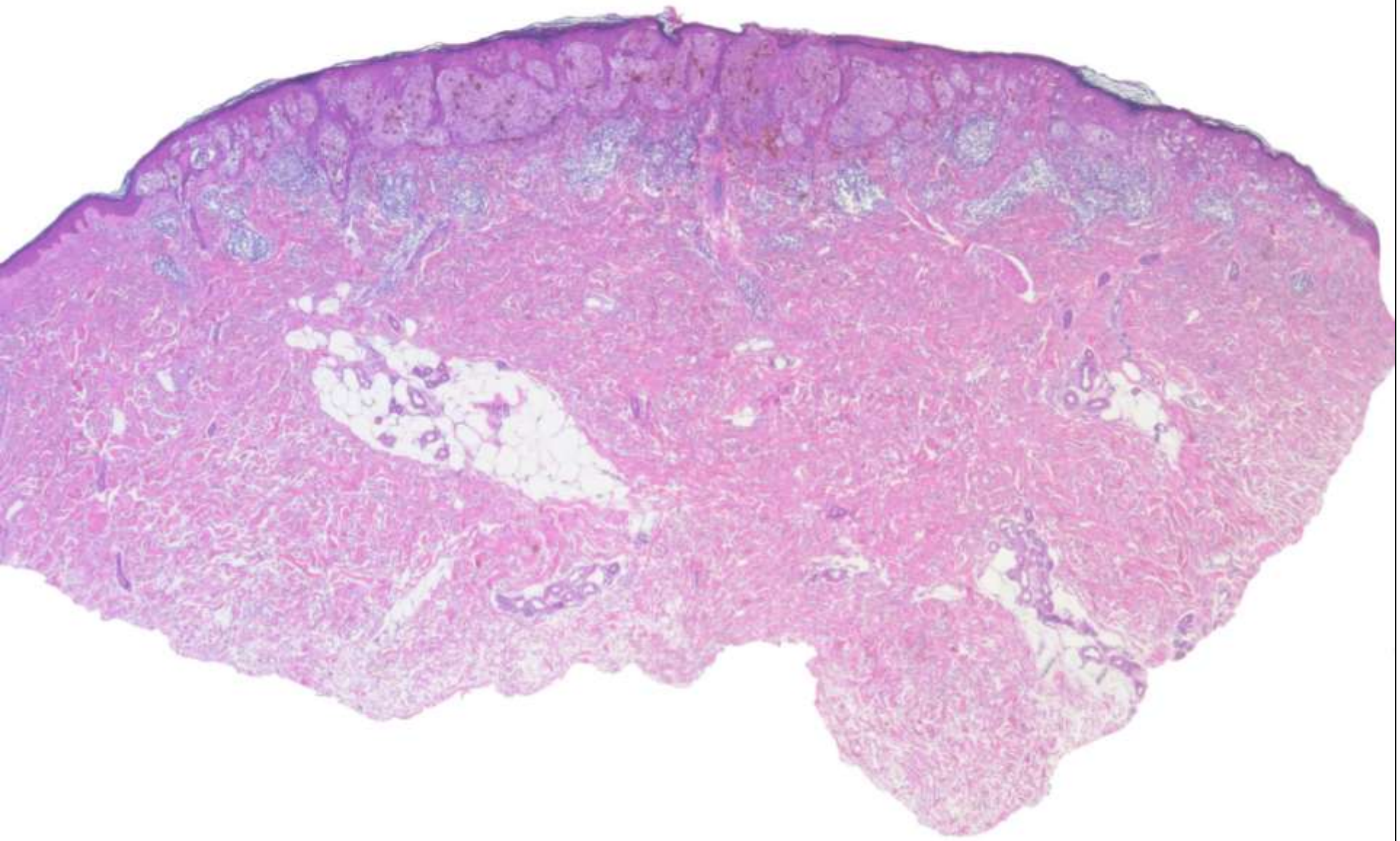
Intermediate lesion

„Atypical
Spitz tumour“

The same is true for this lesion, an “atypical Spitz tumour.” There is only one pattern of growth, one population of cells. Of course, such lesions may be difficult to interpret, but a lesion of which I don’t know what it is is not an “intermediate lesion” but a lesion of which I don’t know what it is.

Woman, 56 y., knee

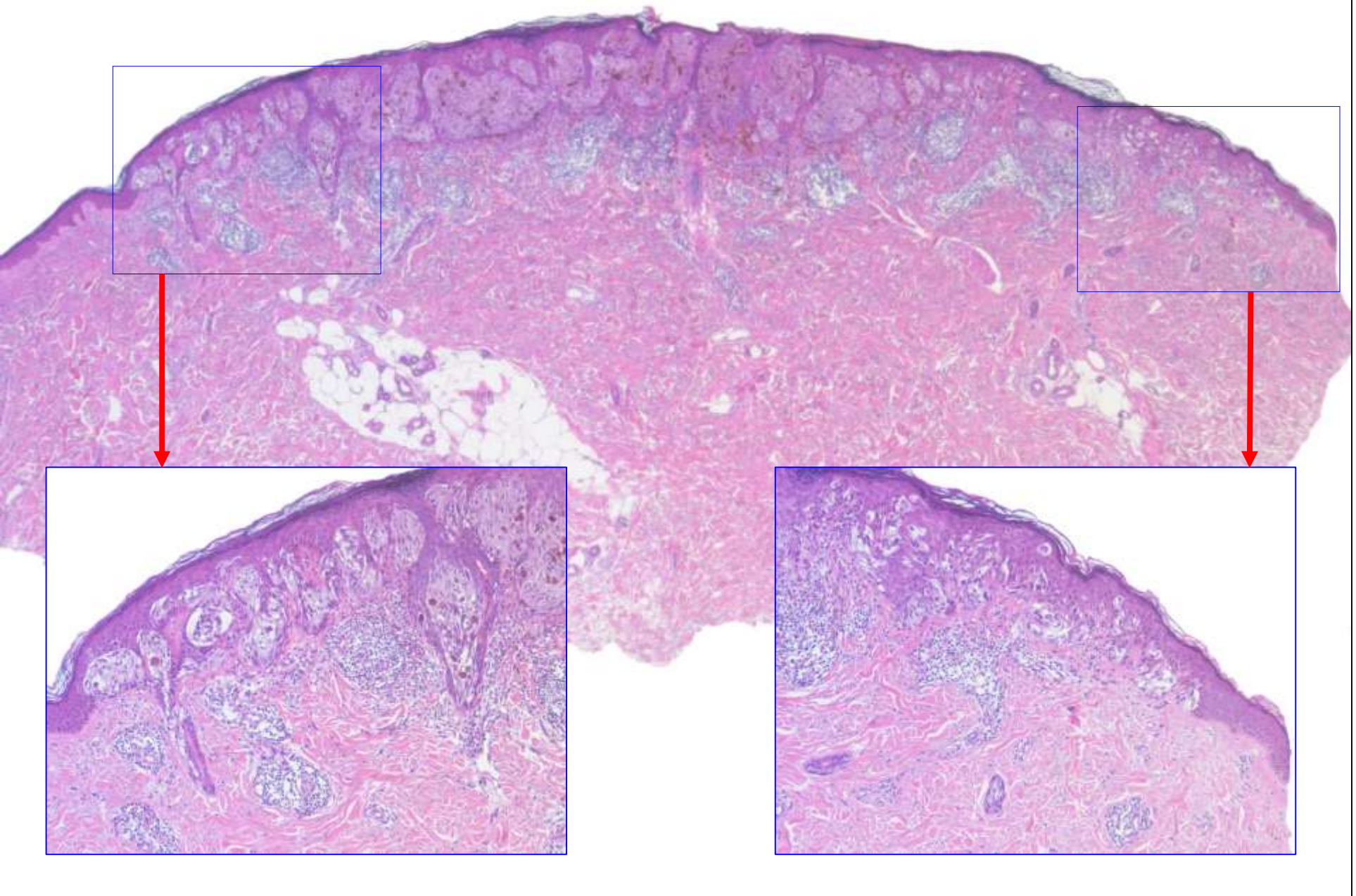
Case 12



Take case 12 of the self assessment, a spitzoid lesion from the knee of a 56 year-old lady, difficult to interpret and within the range of what has been reported as an “atypical Spitz tumour.” It is sharply circumscribed, consists mostly of nests, and melanocytes are distributed evenly.

Woman, 56 y., knee

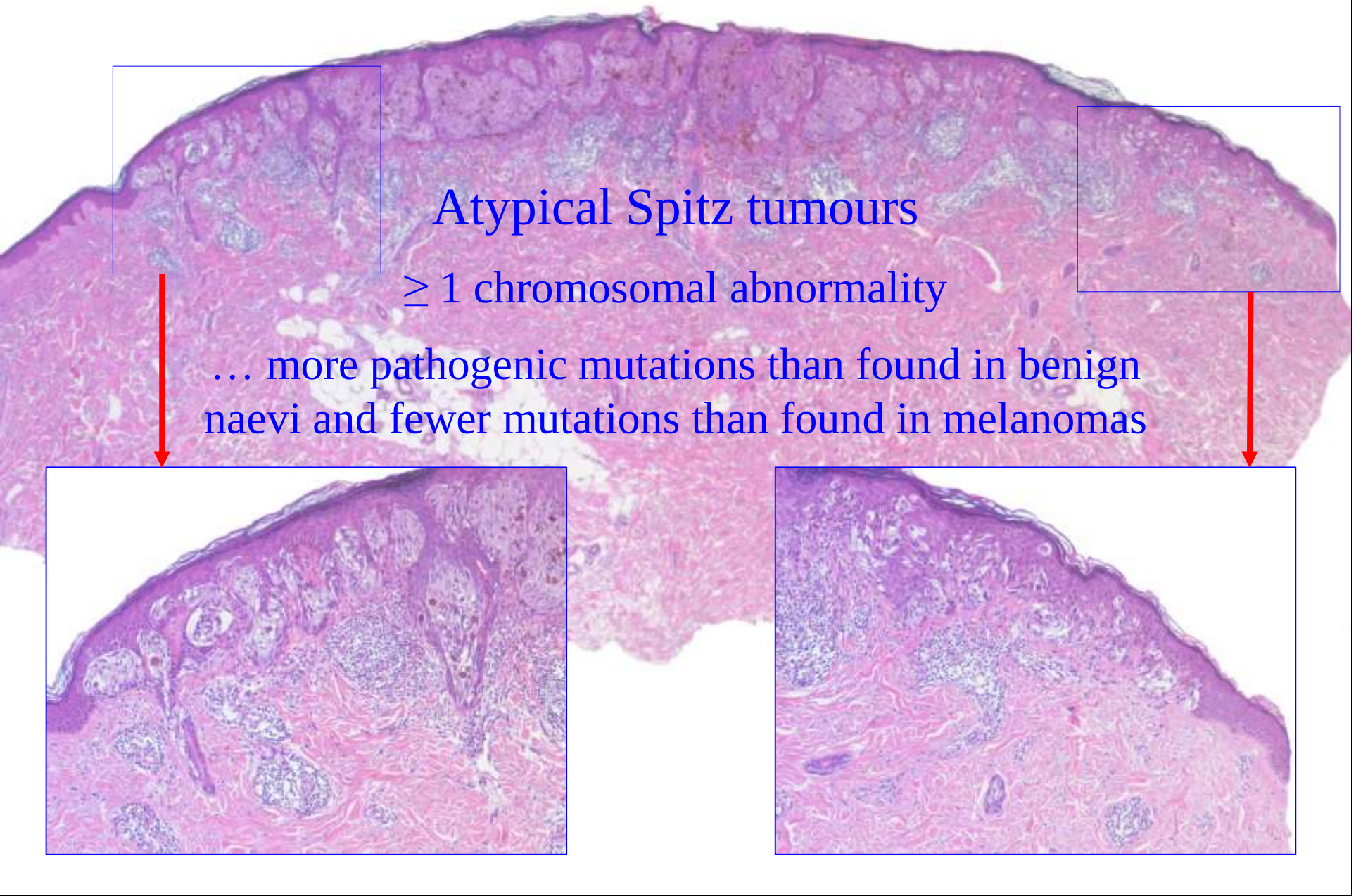
Case 12



However, nests are very large and confluent, and the lesion is asymmetrical, with solitary melanocytes scattered throughout the epidermis at one edge only.

Woman, 56 y., knee

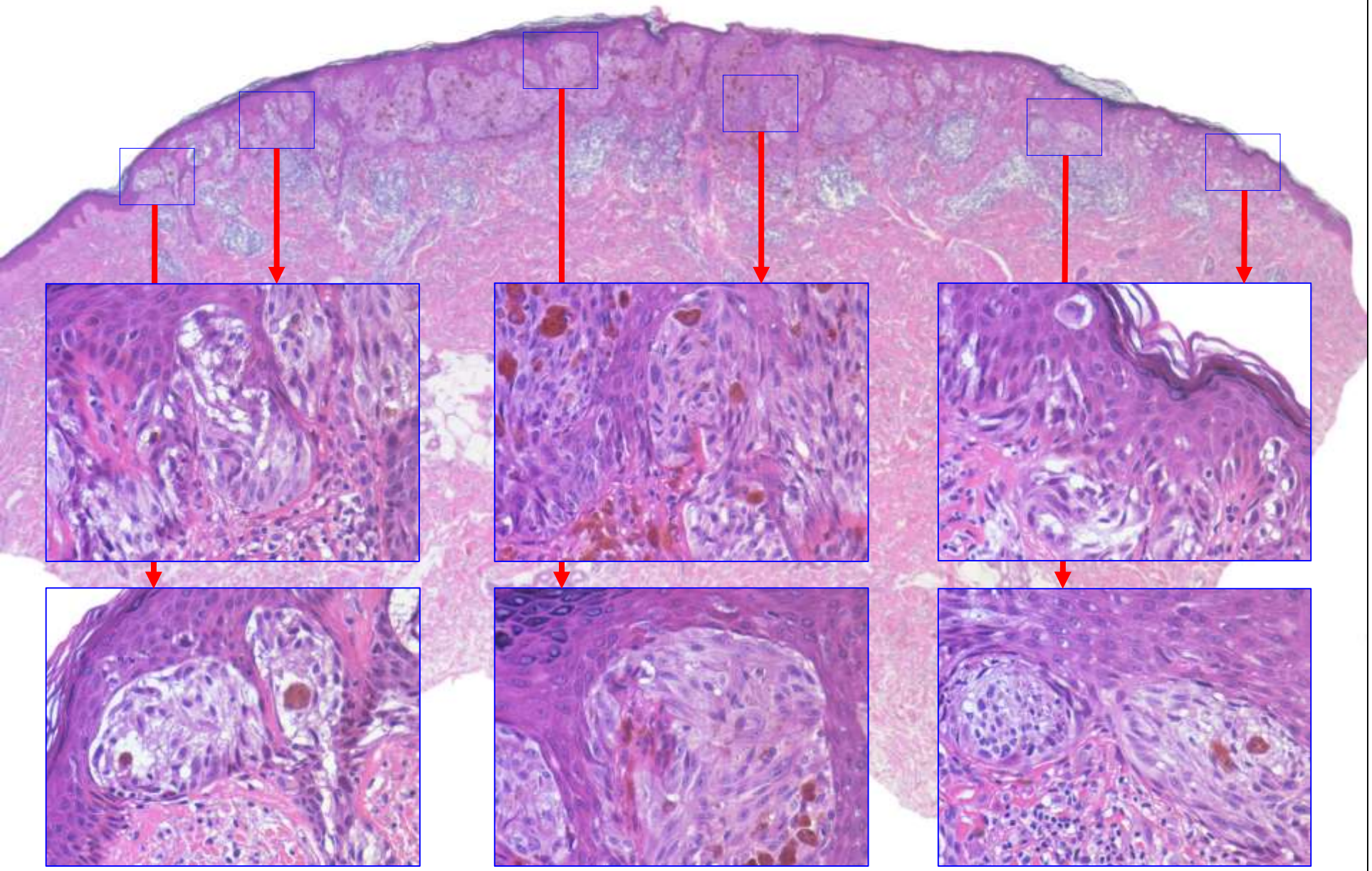
Case 12



According to the WHO classification of melanoma, "atypical Spitz tumours" often have *"≥ 1 chromosomal abnormality"* and are said to belong to a category of neoplasms *"that have more pathogenic mutations than found in benign naevi and fewer mutations than found in melanomas."* This may be true for this individual lesion. But even if this the case and the lesion is "intermediate" in terms of chromosomal abnormalities and maybe even prognosis,

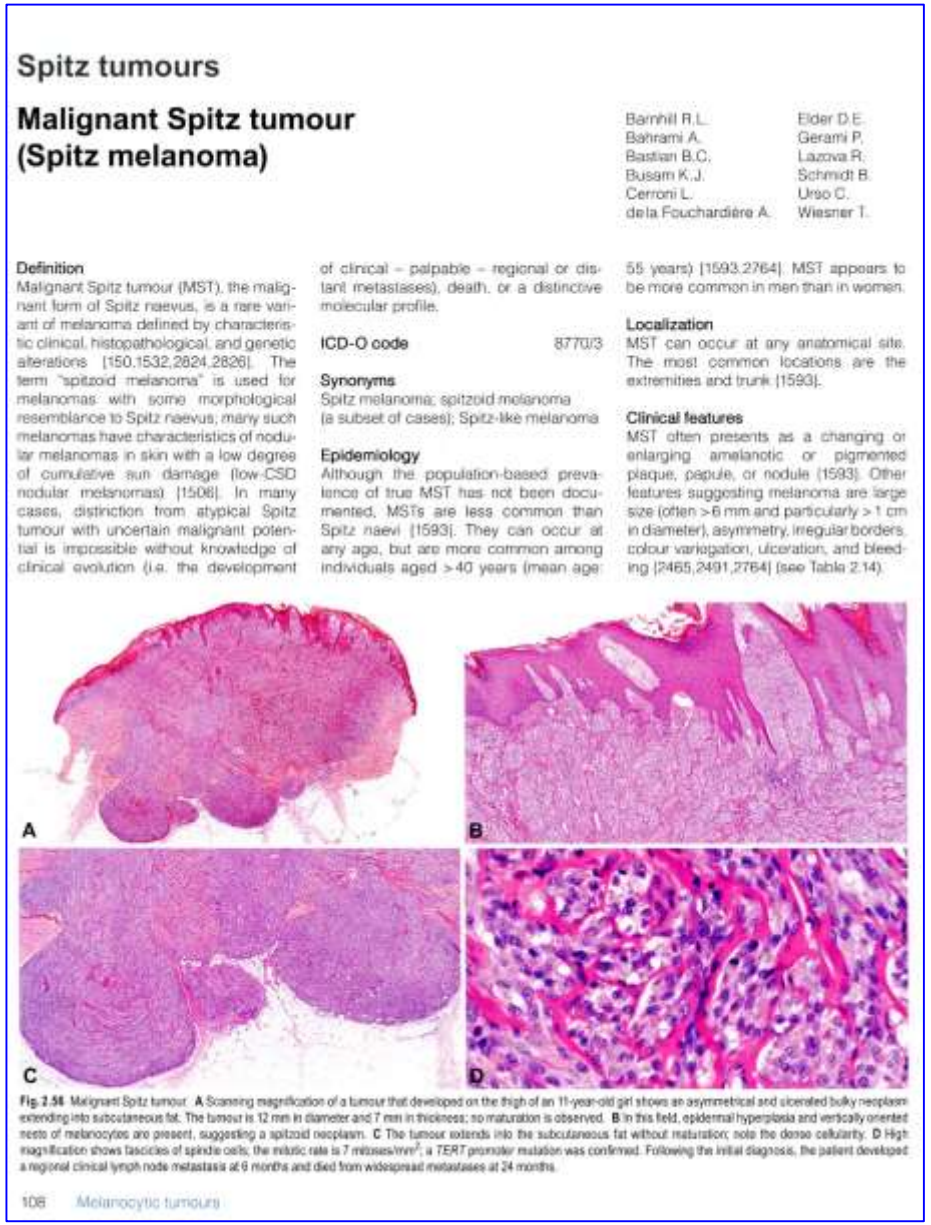
Woman, 56 y., knee

Case 12



it is not immediate in its biologic evolution, starting off as a Spitz nevus and evolving to an “atypical Spitz nevus” through additional genetic changes en route to Spitz melanoma, because it is clearly composed of one population of cells. Those cells are the same everyplace, like siblings, like identical twins.

Is there a category of malignant melanocytic neoplasms with a behavior so favorable that it is intermediate prognostically, just as squamous cell carcinomas of the same size have a prognosis better than melanoma and worse than basal cell carcinoma?



Spitz tumours

Malignant Spitz tumour (Spitz melanoma)

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ICD-O code 8770/3

Synonyms
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Although the population-based prevalence of true MST has not been documented, MSTs are less common than Spitz naevi [1593]. They can occur at any age, but are more common among individuals aged >40 years (mean age: 55 years) [1593,2764]. MST appears to be more common in men than in women.

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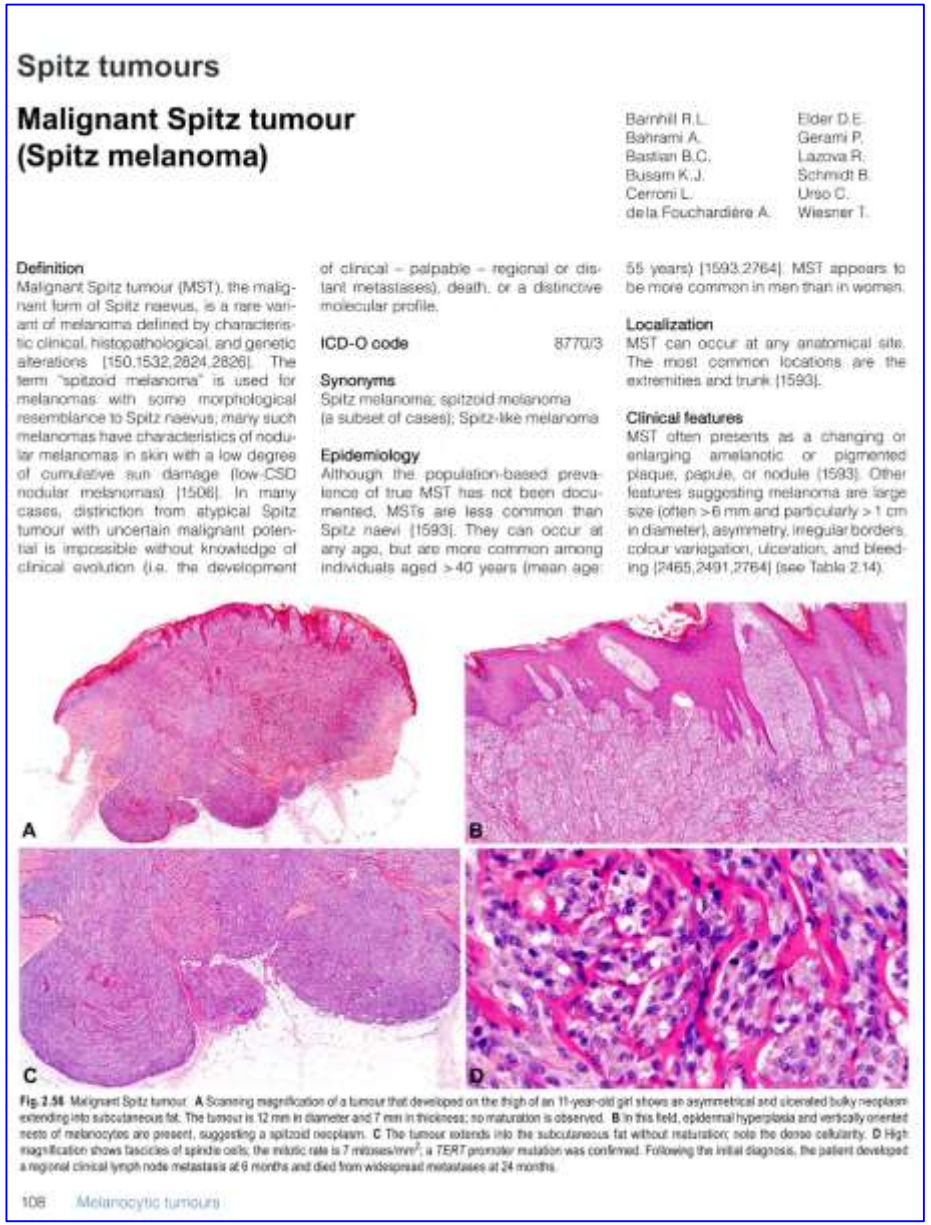
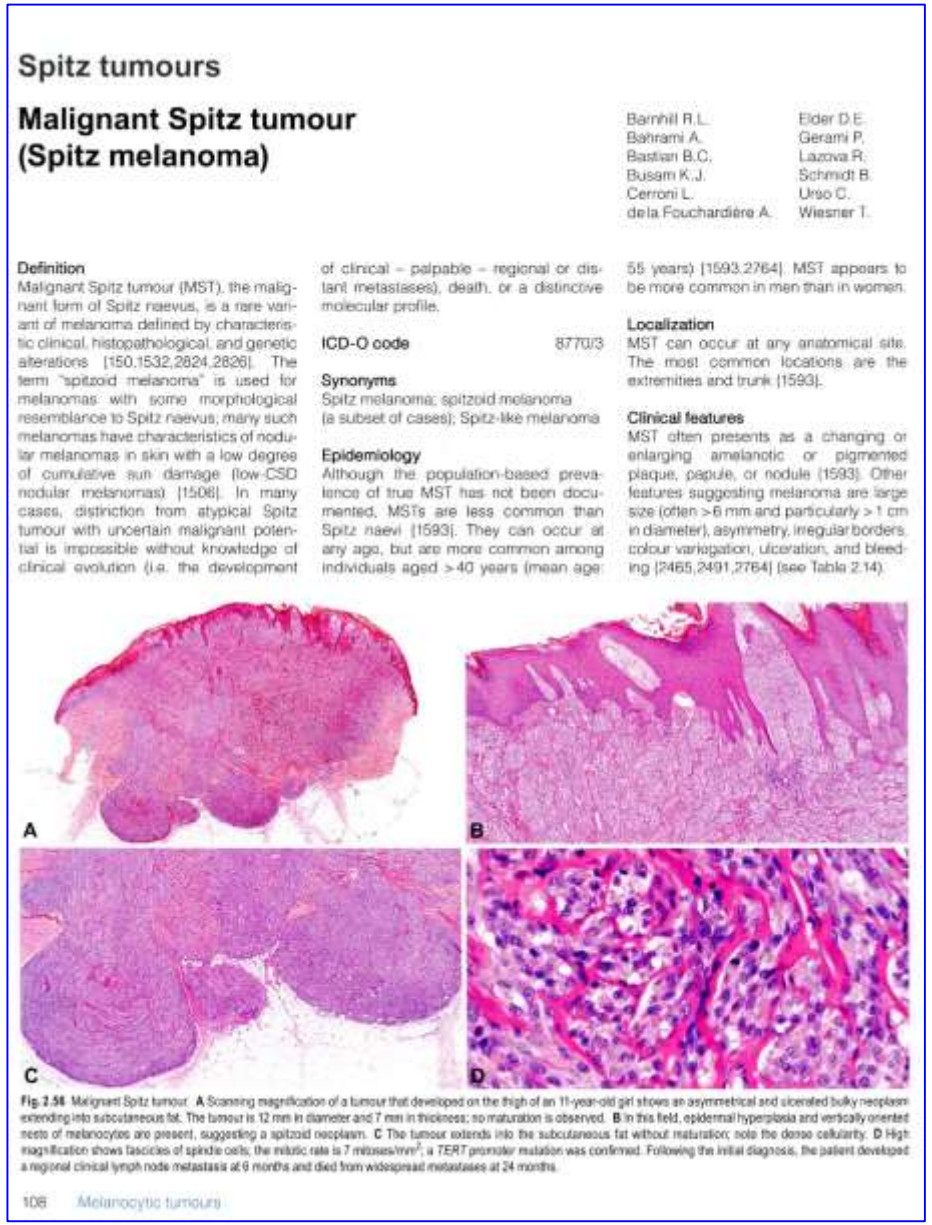
In the WHO classification, this is claimed for Spitz melanoma that is said to be *"usually less aggressive in terms of lethal behaviour than are similarly staged conventional melanomas."* However, the more favourable prognosis may be caused by inclusion of some benign Spitz nevi in statistical analyses.



Death from lesions such as this one has been described repeatedly, and the presumably favorable prognosis has been called in question. Moreover, no definition has ever been forged for “conventional melanoma,” and the definition of “Spitz melanoma” in the current WHO classification is extremely vague,



namely, *“melanomas with some morphological resemblance to Spitz nevus.”*

Can those melanomas be characterized further?

WHO Classification of Skin Tumours

Edited by David E. Elder, Daniela Massi, Richard A. Scolyer, Rein Willemze

Mod Pathol. 2017 May ; 30(5): 640–649. doi:10.1038/modpathol.2016.237.

Spitz nevi and Spitzoid melanomas - Exome sequencing and comparison to conventional melanocytic nevi and melanomas

Rossitza Lazova[1,2,3], Natapol Pornputtapong[2,3], Ruth Halaban[1], Marcus Bosenberg[1,2], Yalai Bai[2], Hao Chai[4], and Michael Krauthammer[2,5]

[1]Department of Dermatology, Yale University School of Medicine, New Haven, CT, 06520-8059

[2]Department of Pathology, Yale University School of Medicine, New Haven, CT, 06520-8059

[4]School of Public Health, Yale University School of Medicine, New Haven, CT, 06520-8059

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Abstract

We performed exome-sequencing of 77 melanocytic specimens composed of Spitz nevi (n=29), Spitzoid melanomas (n=27) and benign melanocytic nevi (n=21), and compared the results to published melanoma sequencing data. Our study highlights the prominent similarity between Spitzoid and conventional melanomas with similar copy number changes and high and equal numbers of ultraviolet-induced coding mutations affecting similar driver genes. Mutations in *MEN1*, *PRKAR1A*, and *DNMT3A* in Spitzoid melanomas may indicate involvement of the protein kinase-A pathway, or a role of DNA methylation in the disease. In addition to activating *HRAS* variants, there were few mutations in Spitz nevi, and few copy number changes other than 11p amplification and chromosome 9 deletions. Similarly, there were no large-scale copy number alterations and few somatic alterations other than activating *BRAF* or *NRAS* mutations in conventional nevi. A presumed melanoma driver mutation ($IDH1^{Arg132Cys}$) was revealed in one of the benign nevi. In conclusion, our exome data show significantly lower somatic mutation burden in both Spitz and conventional nevi compared to their malignant counterparts, and high genetic similarity between Spitzoid and conventional melanoma.

WHO

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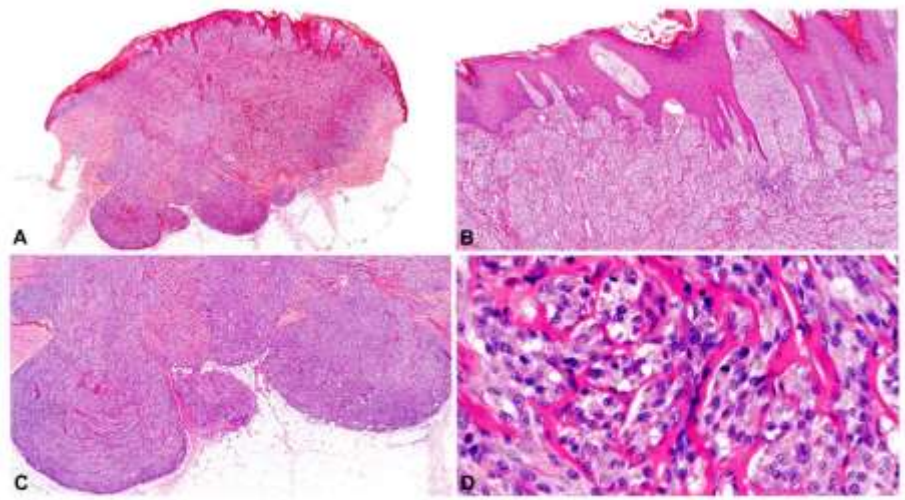

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An attempt was made by Rossitza Lazova and co-workers who, by exome-sequencing, found *"prominent similarity between Spitzoid and conventional melanomas,"* i.e., no significant genetic differences.

WHO Classification of Skin Tumours

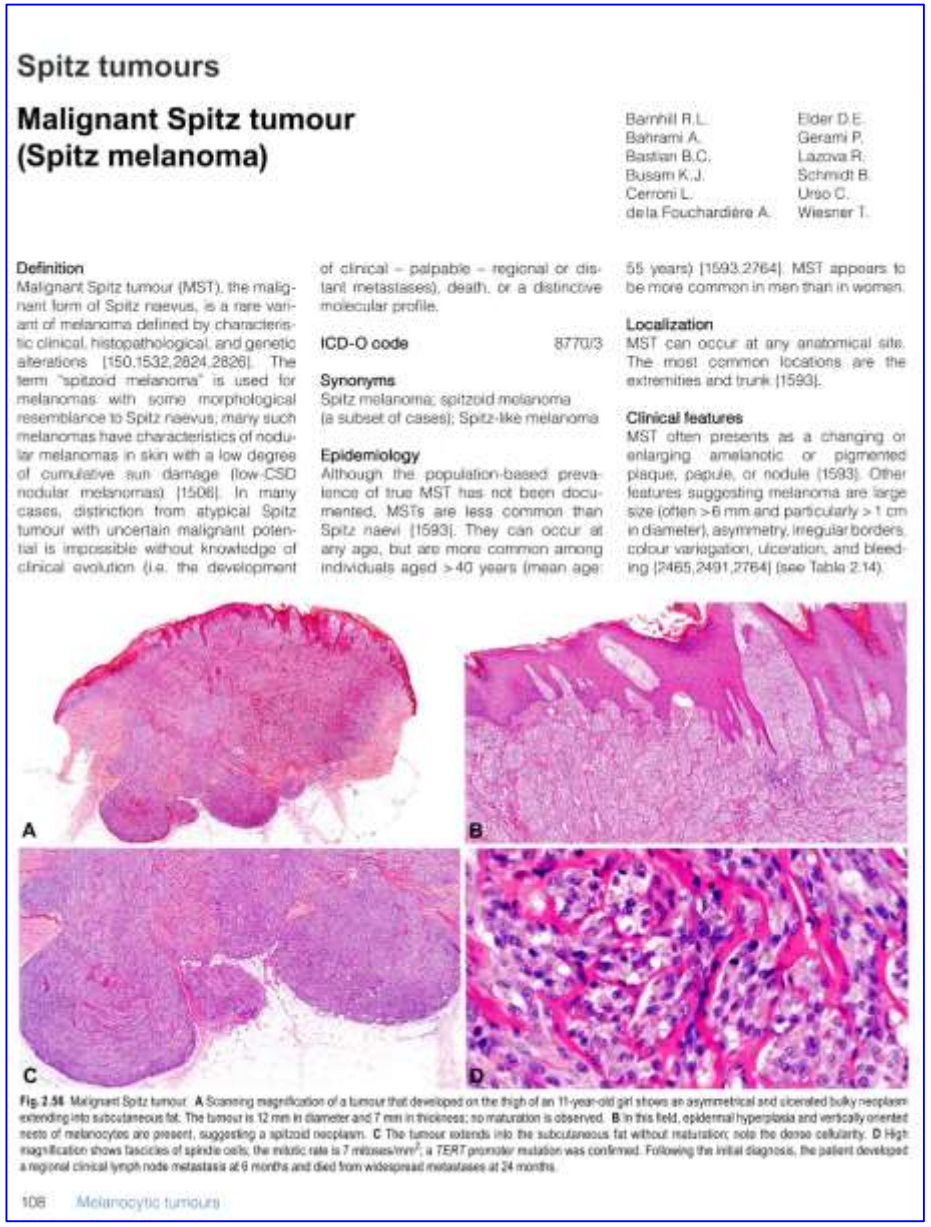
Edited by David E. Elder, Daniela Massi, Richard A. Scolyer, Rein Willemze

Spitz melanoma is a distinct subset of spitzoid melanoma

Raghavan SS, Peternel S, Mully TW, North JP, Pincus LB, LeBoit PE, McCalmont TH, Bastian BC, Yeh I.

Spitz tumors, the spectrum of melanocytic neoplasms extending from Spitz nevi to their malignant counterpart Spitz melanoma, are defined in the 2018 WHO classification of skin tumors by the presence of specific genetic alterations, such as kinase fusions or HRAS mutations. It is unclear what fraction of "spitzoid melanomas" defined solely by their histopathologic features belong to the category of Spitz melanoma or to other melanoma subtypes. While the "spitzoid melanomas" comprising our cohort were enriched for bona fide Spitz melanomas, the majority of melanomas fell outside of the genetically defined category of Spitz melanomas, indicating that histomorphology is an unreliable predictor of Spitz lineage (Mod Pathol 2020).

WHO



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In response, the group of Boris Bastian examined spitzoid melanomas, found the supposedly typical genomic hallmarks of Spitz lesions in only few of them and concluded that *"histopathology is an unreliable predictor of Spitz lineage."*

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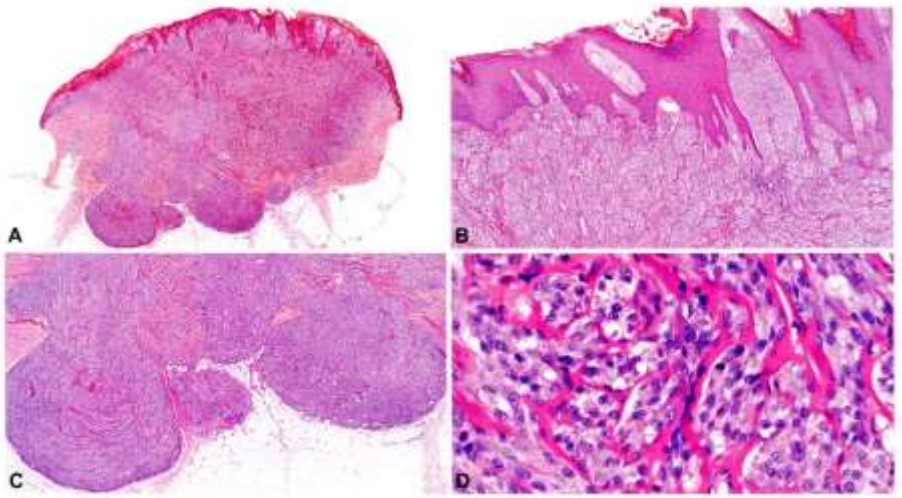

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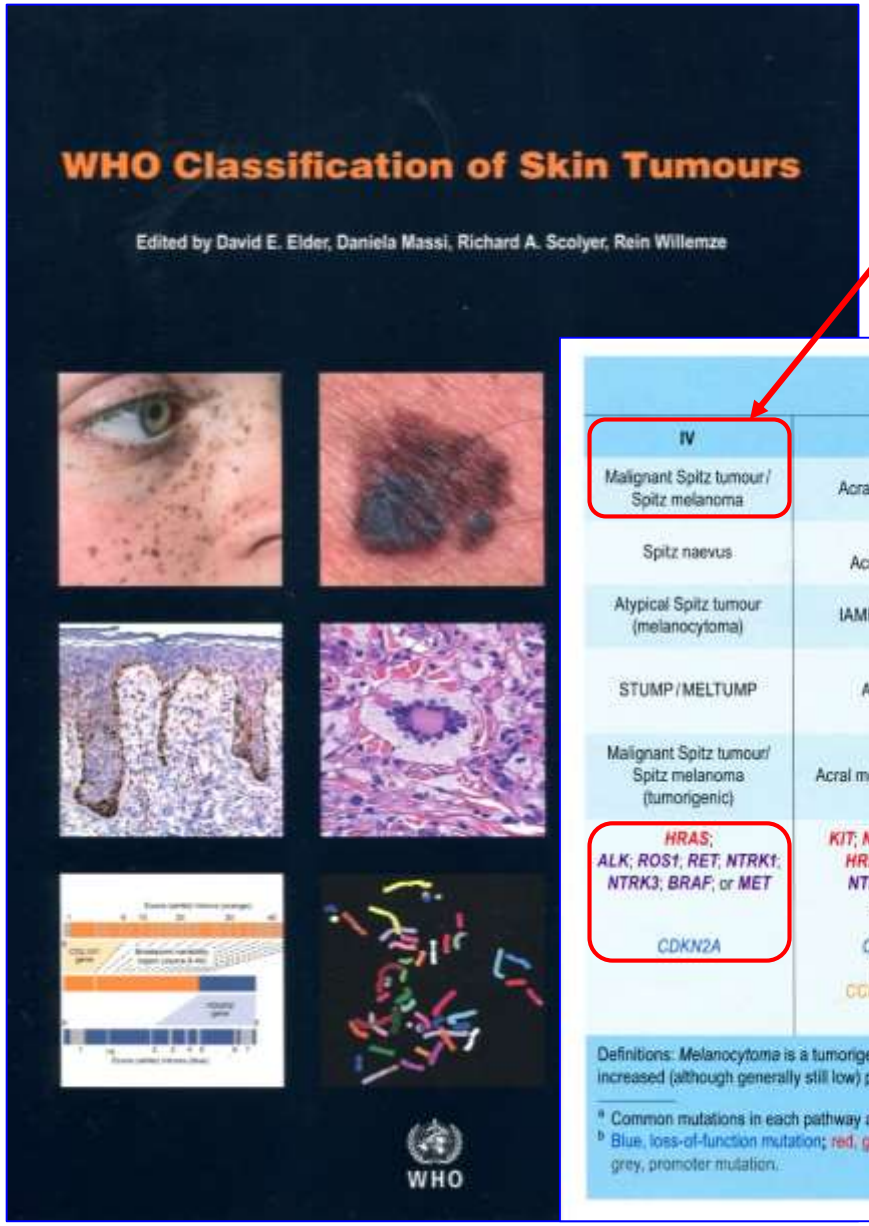
In other words, according to them, Spitz lineage has nothing to do with the definition of Spitz melanoma given in the WHO classification, and there is no correlation of variables across several hierarchical levels as a prerequisite for recognition of any distinct biologic process.



Pathway I:	Low-CSD melanoma/superficial spreading melanoma
Pathway II:	High-CSD melanoma/lentigo maligna melanoma
Pathway III:	Desmoplastic melanoma
Pathway IV:	Malignant Spitz tumour (Spitz melanoma)
Pathway V:	Acral melanoma

Low to no (or variable/incidental) UV radiation exposure / CSD					
IV	**V**	**VI**	**VII**	**VIII**	**IX**
Malignant Spitz tumour / Spitz melanoma	Acral melanoma	Mucosal melanoma	Melanoma in CN	Melanoma in BN	Uveal melanoma
Spitz naevus	? Acral naevus	? Melanosis	CN	Blue naevus	? Naevus
Atypical Spitz tumour (melanocytoma)	IAMP / dysplasia	Atypical melanosis / dysplasia / IAMPUS	Nodule in CN (melanocytoma)	(Atypical) CBN (melanocytoma)	?
STUMP / MELTUMP	Acral MIS	Mucosal MIS	MIS in CN	Atypical CBN	?
Malignant Spitz tumour/ Spitz melanoma (tumorigenic)	Acral melanoma (VGP)	Mucosal lentiginous melanoma (VGP)	Melanoma in CN (tumorigenic)	Melanoma in blue naevus (tumorigenic)	Uveal melanoma
HRAS*; *ALK*; *ROS1*; *RET*; *NTRK1*; *NTRK3*; *BRAF*; or *MET *CDKN2A*	***KIT*; *NRAS*; *BRAF*; *HRAS*; *KRAS*; *NTRK3*; *ALK*; or *NF1*** *CDKN2A*; *TERT*; *CCND1*; *GAB2*	***KIT*, *NRAS*, *KRAS*, or *BRAF*** ***NF1***; *CDKN2A*; *SF3B1*; *CCND1*; *CDK4*; *MDM2*	***NRAS*; BRAF p.V600E (small lesions); or *BRAF*** 	***GNAQ*; *GNA11*; or *CYSLTR2*** *BAP1*; *EIF1AX*; *SF3B1*	***GNAQ*, *GNA11*, *CYSLTR2*, or *PLCB4*** *BAP1*; *SF3B1*; *EIF1AX*

Definitions: *Melanocytoma* is a tumorigenic neoplasm of melanocytes that generally has increased cellularity and/or atypia (compared with a common naevus) and an increased (although generally still low) probability of neoplastic progression; *tumorigenic* means forming a mass of neoplastic cells.

[a] Common mutations in each pathway are listed; mutations already identified in benign or borderline low lesions are shown in bold.
[b] Blue, loss-of-function mutation; red, gain-of-function mutation; green, change-of-function mutation; orange, amplification; purple, rearrangement; grey, promoter mutation.

Nonetheless, Spitz melanoma is presented as a distinct “pathway” of melanoma with a characteristic genomic profile in the WHO classification. Moreover, that “pathway” is claimed

Pathway I:	Low-CSD melanoma/superficial spreading melanoma
Pathway II:	High-CSD melanoma/lentigo maligna melanoma
Pathway III:	Desmoplastic melanoma
Pathway IV:	Malignant Spitz tumour (Spitz melanoma)
Pathway V:	Acral melanoma

Low to no (or variable/incidental) UV radiation exposure / CSD

IV	V	VI	VII	VIII	IX
Malignant Spitz tumour / Spitz melanoma	Acral melanoma	Mucosal melanoma	Melanoma in CN	Melanoma in BN	Uveal melanoma
Spitz naevus	? Acral naevus	? Melanosis	CN	Blue naevus	? Naevus
Atypical Spitz tumour (melanocytoma)	IAMP / dysplasia	Atypical melanosis / dysplasia / IAMPUS	Nodule in CN (melanocytoma)	(Atypical) CBN (melanocytoma)	?
STUMP / MELTUMP	Acral MIS	Mucosal MIS	MIS in CN	Atypical CBN	?
Malignant Spitz tumour/ Spitz melanoma (tumorigenic)	Acral melanoma (VGP)	Mucosal lentiginous melanoma (VGP)	Melanoma in CN (tumorigenic)	Melanoma in blue naevus (tumorigenic)	Uveal melanoma
HRAS*; *ALK*; *ROS1*; *RET*; *NTRK1*; *NTRK3*; *BRAF*; or *MET	***KIT*; *NRAS*; *BRAF*; *HRAS*; *KRAS*; *NTRK3*; *ALK*; or *NF1***	***KIT*, *NRAS*, *KRAS*, or *BRAF***	***NRAS*; BRAF p.V600E (small lesions); or *BRAF***	***GNAQ*; *GNA11*; or *CYSLTR2***	***GNAQ*, *GNA11*, *CYSLTR2*, or *PLCB4***
CDKN2A	*CDKN2A*; *TERT*; *CCND1*; *GAB2*	***NF1***; *CDKN2A*; *SF3B1*; *CCND1*; *CDK4*; *MDM2*		*BAP1*; *EIF1AX*; *SF3B1*	*BAP1*; *SF3B1*; *EIF1AX*

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to start with Spitz nevus and eventuate to “atypical Spitz tumour,” until finally reaching the endpoint of Spitz melanoma, as if this were a progressive process. How can those contradictions be explained?

The reason is that the authors fell victim to an old mistake of Clark that has been perpetuated with strong force by members of his school, namely, to confuse multistep carcinogenesis on a genetic level with the evolution of lesions histopathologic and clinical.

A Study of Tumor Progression:

The Precursor Lesions of Superficial Spreading and Nodular Melanoma

WALLACE H. CLARK, JR, MD, DAVID E. ELDER, MD, ChB,
DUPONT GUERRY, IV, MD, MARTIN N. EPSTEIN, PhD,* MARK H. GREENE, MD,†
AND MARIE VAN HORN, BS

Six evident lesional steps of tumor progression form the neoplastic system that affects the human epidermal melanocyte: 1) the common acquired melanocytic nevus; 2) a melanocytic nevus with lentiginous melanocytic hyperplasia, i.e., aberrant differentiation; 3) a melanocytic nevus with aberrant differentiation and melanocytic nuclear atypia, i.e., melanocytic dysplasia; 4) the radial growth phase of primary melanoma; 5) the vertical growth phase of primary melanoma; and 6) metastatic melanoma. The common acquired melanocytic nevus is viewed as a focal proliferation of melanocytes, destined in most instances to follow a programmed pathway of differentiation that leads to disappearance of the nevus. If the pathway of differentiation is not followed, characteristic lesions result, and such lesions are regarded as the formal histogenetic precursors of melanoma. Such a de-

acteristic of metastases. It is postulated
tical growth phase are those that give ri
lesional step of tumor progression is m
tumor progression described in this pa
paradigm for neoplasia, and from this model a sequence of generic lesions applicable to neoplastic development in general is presented. These generic steps of tumor progression are 1) a selective focal proliferation of structurally normal cells (a benign tumor); 2) an abnormal pattern of hyperplasia (aberrant differentiation); 3) an abnormal pattern of hyperplasia and random cytologic atypia (aberrant differentiation and the appearance of cells with nuclear atypia); 4) primary cancer without competence for metastasis; 5) primary cancer with competence for metastasis; and 6) metastatic cancer. HUM PATHOL 15:1147–1165, 1984.

Six evident lesional steps of tumor progression form the neoplastic system that affects the human epidermal melanocyte: 1) the common acquired melanocytic nevus; 2) a melanocytic nevus with lentiginous melanocytic hyperplasia, i.e., aberrant differentiation; 3) a melanocytic nevus with aberrant differentiation and melanocytic nuclear atypia, i.e., melanocytic dysplasia; 4) the radial growth phase of primary melanoma; 5) the vertical growth phase of primary melanoma; and 6) metastatic melanoma.

to the directional growth of the radial growth phase. As a rule, the cells of the vertical growth phase grow in an expansile fashion, expansile as a balloon expands: a growth form char-

plasia is exemplified by the first evident lesion of the system: a focal proliferation in the basilar epidermal

In a study on tumor progression, Clark envisioned a multistep evolution of lesions, from a “common acquired melanocytic nevus” via melanocytic dysplasia and the so-called radial and vertical growth phase of primary melanoma to metastatic melanoma, as if each of those steps resulted from an additional genomic change. This model was defended against all common sense.

The American Journal of Dermatopathology 11(4): 387–389, 1989

Malignant Melanoma in Light of the Multistep Theory of Neoplasia*

Arkadi M. Rywlin, M.D.

Malignant melanoma (MM) appears to be an experiment of nature that supports the multistep theory of neoplasia (1). According to this theory, the transformation of a normal cell to a malignant cell requires several steps. A cell can be considered completely transformed when it has acquired the capacity to invade surrounding tissue and to metastasize. Scientists working with tissue cultures define complete transformation of cells as loss of contact inhibition and acquisition of immortality. Since malignant cells (fully transformed cells) are genetically unstable, they may undergo further morphologic and functional changes, giving rise to the heterogeneity of the cells making up a malignant neoplasm (2). Our understanding of how cells acquire the capacity to invade and metastasize is limited. ders between hyperplasia and neoplasia in situ cannot be determined morphologically at the present state of our knowledge. The multistep theory of neoplasia makes the definition of a malignancy in situ easy. Malignancy in situ is a condition in which one or several cells have acquired the ability to invade and metastasize, but have not as yet exercised these options. The problem is that malignancy in situ, when defined as above, is not diagnosable because we cannot recognize these fully transformed cells until they actually invade the underlying tissue. We have no marker to inform us that all the genetic and epigenetic events that render a cell capable of invasion have occurred. The arbitrary definition of carcinoma in situ as atypia involving the full thickness of the epithelium is obviously not jus-

may not occur. The intraepithelial containment of the atypical cells therefore appears not to be due to surveillance by the immune system, but to the lack of complete transformation of the cells.

ible whereas neoplasia is irreversible. This continuum of changes can be observed in the skin, oral mucous membrane, bronchial mucosa, vocal cords, breast, uterine cervix, endometrium, prostate, and other areas. From experimental pathology, it is

additional genetic or epigenetic events that may or may not occur. The intraepithelial containment of the atypical cells therefore appears not to be due to surveillance by the immune system, but to the lack of complete transformation of the cells.

For example, *"the intraepithelial containment of atypical cells"* in melanoma in situ was said by Rywlin *"to be due … to the lack of complete transformation of the cells,"*

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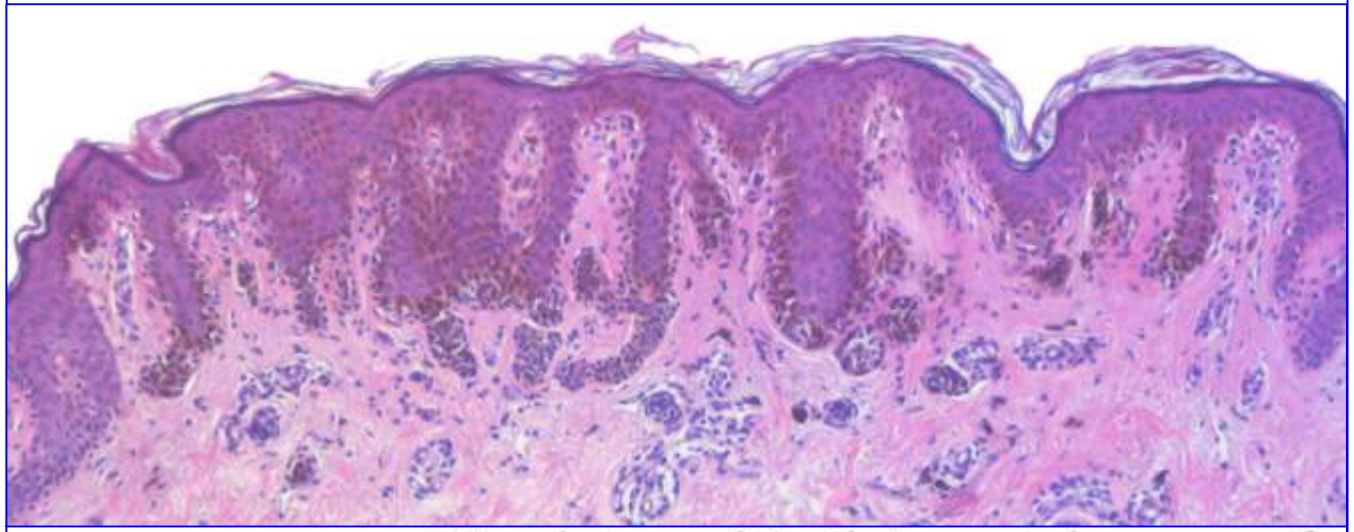

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although every cell of a banal nevus is known to be capable of crossing the basement membrane.

ORIGINAL ARTICLE

The Genetic Evolution of Melanoma from Precursor Lesions

A. Hunter Shain, Ph.D., Iwei Yeh, M.D., Ph.D., Ivanka Kovalyshyn, D.O., Aravindhan Sriharan, M.D., Eric Talevich, Ph.D., Alexander Gagnon, B.A., Reinhard Dummer, M.D., Jeffrey North, M.D., Laura Pincus, M.D., Beth Ruben, M.D., William Rickaby, M.B., Ch.B., Corrado D'Arrigo, M.B., Ch.B., Ph.D., Alistair Robson, F.R.C.Path., and Boris C. Bastian, M.D.

ABSTRACT

BACKGROUND

The pathogenic mutations in melanoma have been largely catalogued; however, the order of their occurrence is not known.

METHODS

We sequenced 293 cancer-relevant genes in 150 areas of 37 primary melanomas and their adjacent precursor lesions. The histopathological spectrum of these areas included unequivocally benign lesions, intermediate lesions, and intraepidermal or invasive melanomas.

RESULTS

Precursor lesions were initiated by mutations of genes that are known to activate the mitogen-activated protein kinase pathway. Unequivocally benign lesions harbored *BRAF* V600E mutations exclusively, whereas those categorized as intermediate were enriched for *NRAS* mutations and additional driver mutations. A total of 77% of areas of intermediate lesions and melanomas in situ harbored *TERT* promoter mutations, a finding that indicates that these mutations are selected at an unexpectedly early stage of the neoplastic progression. Biallelic inactivation of *CDKN2A* emerged exclusively in invasive melanomas. *PTEN* and *TP53* mutations were found only in advanced primary melanomas. The point-mutation burden increased from benign through intermediate lesions to melanoma, with a strong signature of the effects of ultraviolet radiation detectable at all evolutionary stages. Copy-number alterations became prevalent only in invasive melanomas. Tumor heterogeneity became apparent in the form of genetically distinct subpopulations as melanomas progressed.

CONCLUSIONS

Our study defined the succession of genetic alterations during melanoma progression, showing distinct evolutionary trajectories for different melanoma subtypes. It identified an intermediate category of melanocytic neoplasia, characterized by the presence of more than one pathogenic genetic alteration and distinctive histopathological features. Finally, our study implicated ultraviolet radiation as a major factor in both the initiation and progression of melanoma. (Funded by the National Institutes of Health and others.)

From the Departments of Dermatology and Pathology (A.H.S., I.Y., E.T., A.G., J.N., L.P., B.R., B.C.B.) and the Helen Diller Family Comprehensive Cancer Center (A.H.S., I.Y., E.T., A.G., B.C.B.), University of California, San Francisco (UCSF), San Francisco; the Departments of Dermatology and Pathology, Cleveland Clinic, Cleveland (I.K.); the Department of Pathology, Orlando Health, Orlando, FL (A.S.); the Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland (R.D.); and the Department of Dermatology, Dorset County Hospital, Dorchester (C.D.), and the Department of Dermatology, St. John's Institute of Dermatology, London (W.R., A.R.) — both in the United Kingdom. Address reprint requests to Dr. Bastian at the UCSF Dermatopathology Service, 1701 Divisadero St., Suite 280, San Francisco, CA 94115, or at boris.bastian@ucsf.edu.

N Engl J Med 2015;373:1926-36.
DOI: 10.1056/NEJMoa1502583

Based on those ideas, Shain and co-workers in 2015 conducted a study concerning "the genetic evolution of melanoma from precursor lesions" in which they examined the rare exception of melanoma arising on a nevus. In other words, the conclusion that melanonas develop on "precursor lesions" was already part of the study design.

ORIGINAL ARTICLE

The Genetic Evolution of Melanoma from Precursor Lesions

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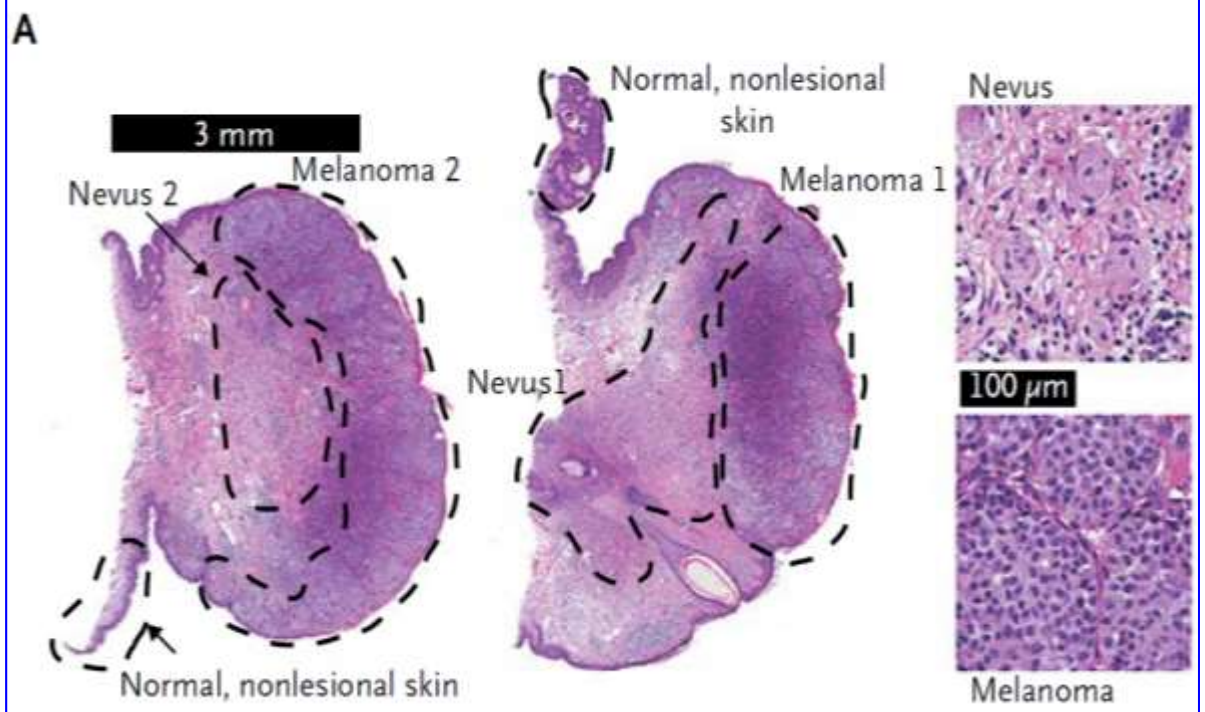

In those selected tumors, the authors studied genetic changes at various sites, and in areas that could not be assigned clearly to either the nevus or the melanoma compartment, they found a slightly enhanced frequency of mutations.

ORIGINAL ARTICLE

The Genetic Evolution of Melanoma from Precursor Lesions

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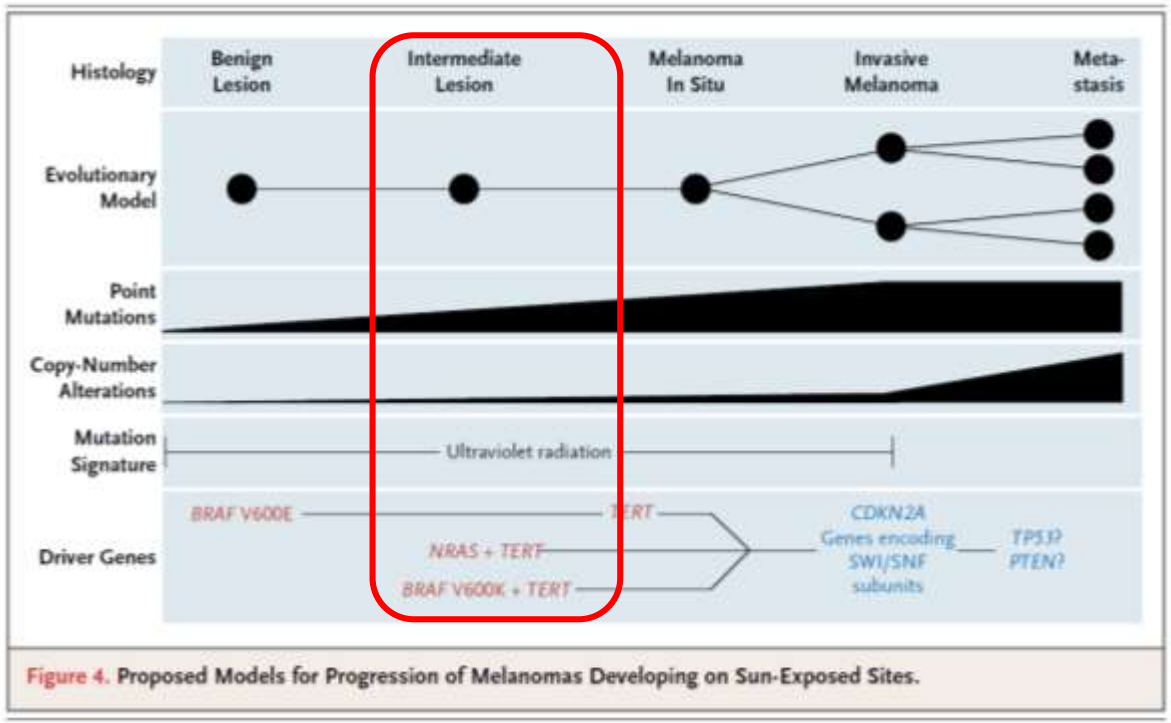
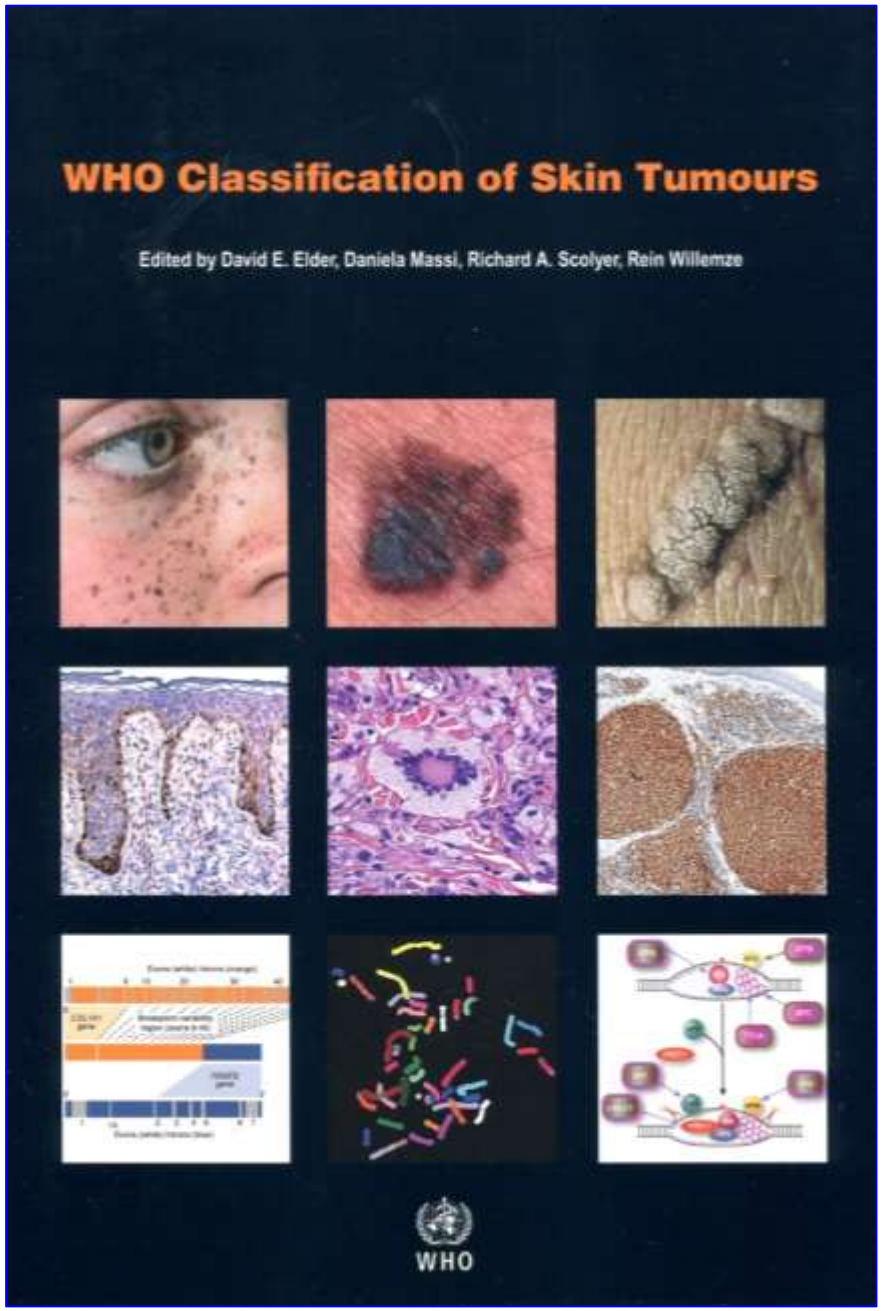


Figure 4. Proposed Models for Progression of Melanomas Developing on Sun-Exposed Sites.

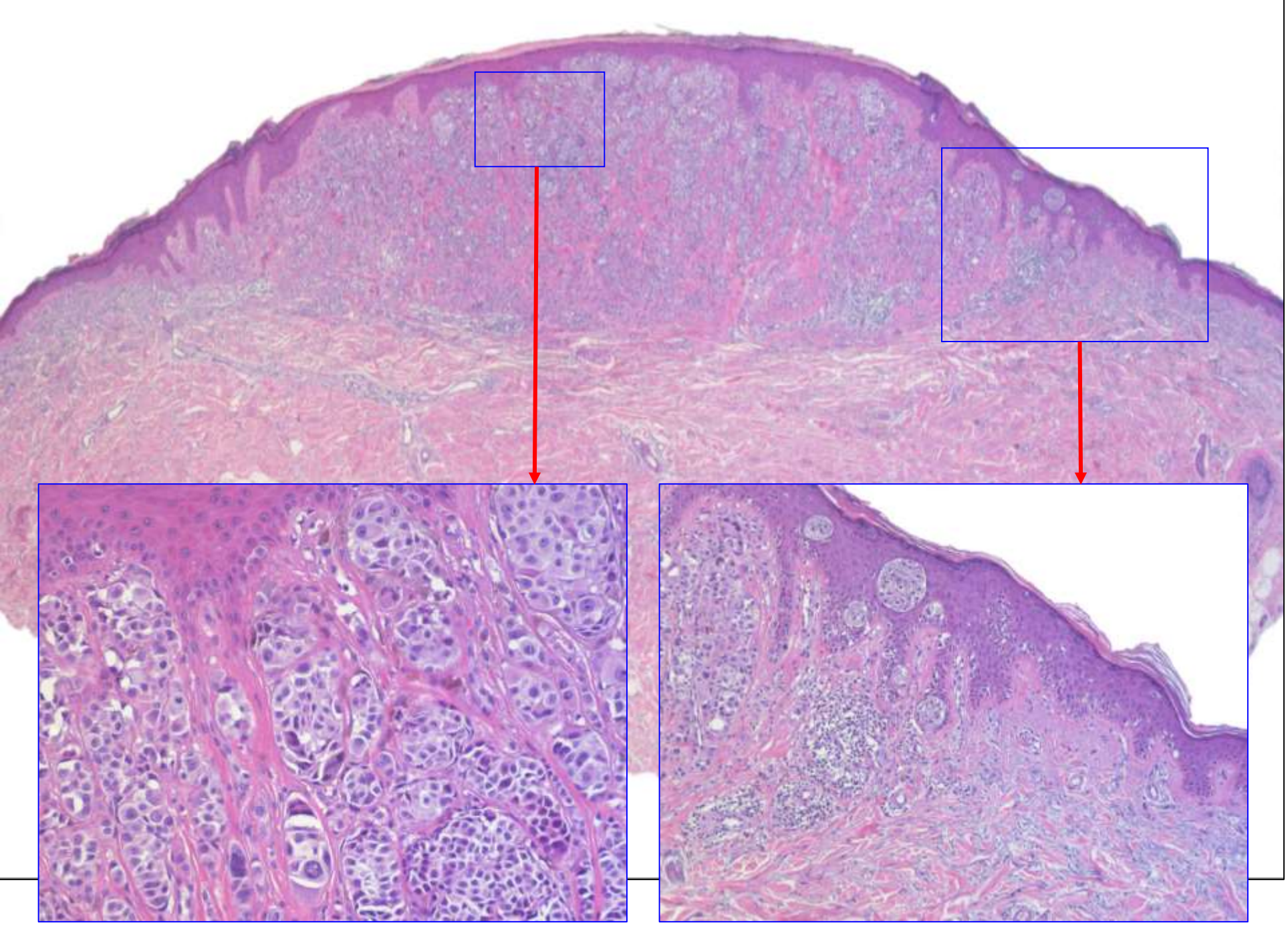
This was their only evidence for the existence of "intermediate lesions." They claimed that cells of "intermediate lesions" were only "partially transformed,"



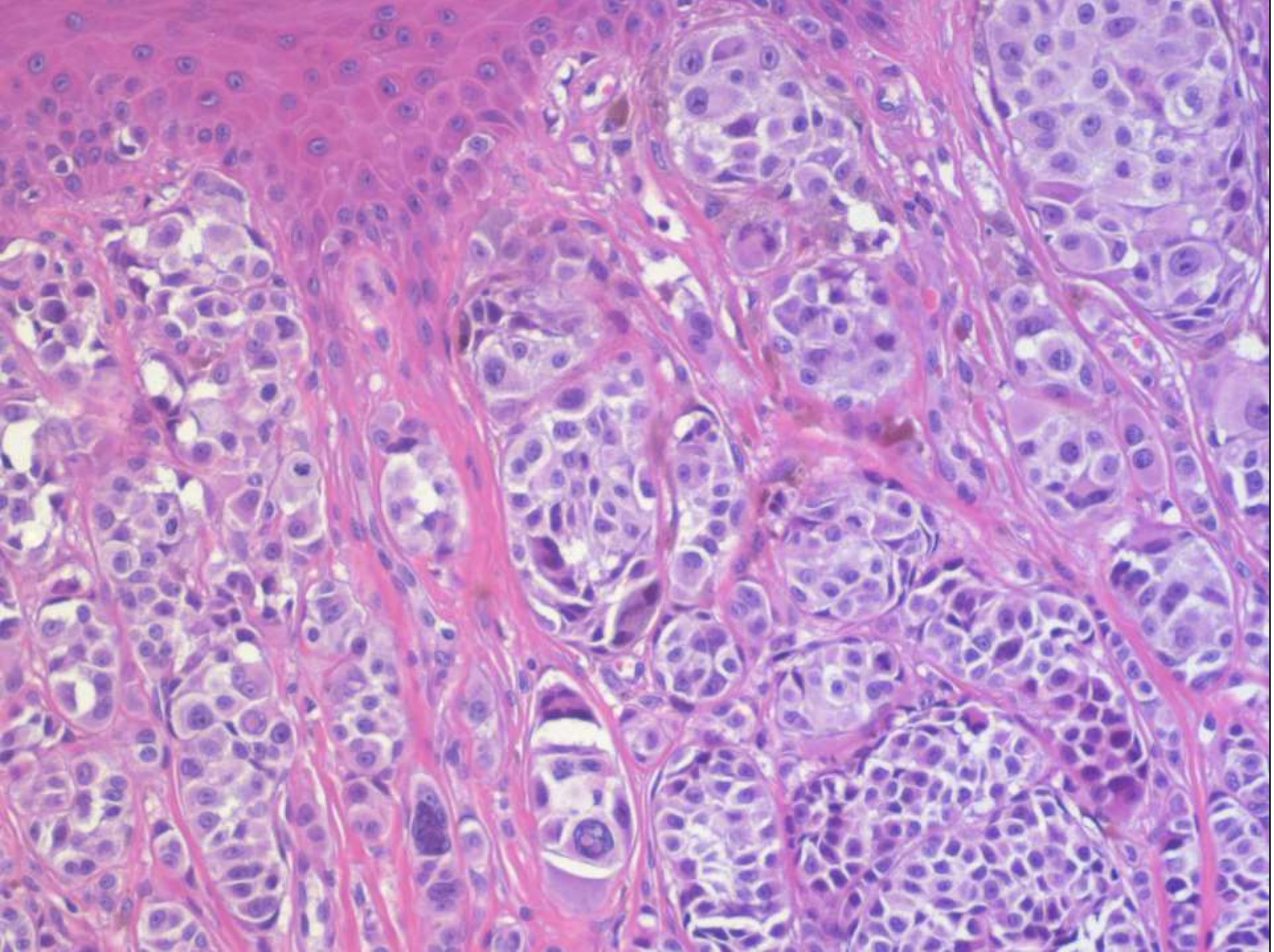
Naevi can thus be melanoma precursors because they are composed of partially transformed melanocytes that already harbour one of the multiple mutations required for melanoma formation. The numerical expansion of the original melanocyte that first acquired the oncogenic mutation into hundreds of thousands of daughter cells carrying the same mutation then increases the probability of one of those cells acquiring an additional pathogenic mutation on top of the first one. UV irradiation of naevus cells is the major driver generating these secondary and subsequent mutations that ultimately lead to melanoma {2394}.

Categories of neoplasms are now emerging that have more pathogenic mutations than found in benign naevi and fewer mutations than found in melanomas; the atypical spitzoid proliferations with

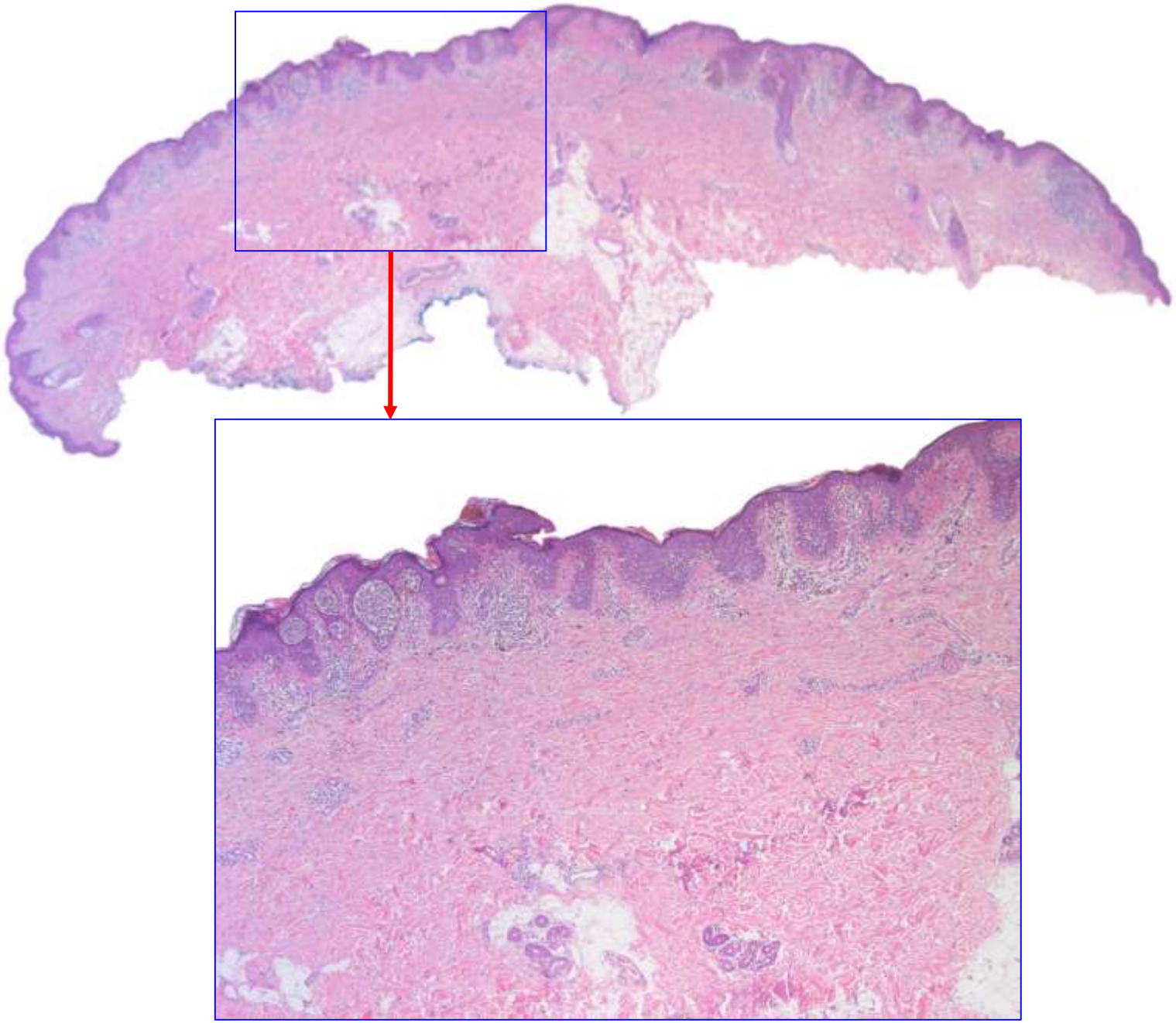
a notion adopted in the current WHO classification, and, of course, they were right. But when is a cell “fully transformed”? With five, fifty or hundred mutations?



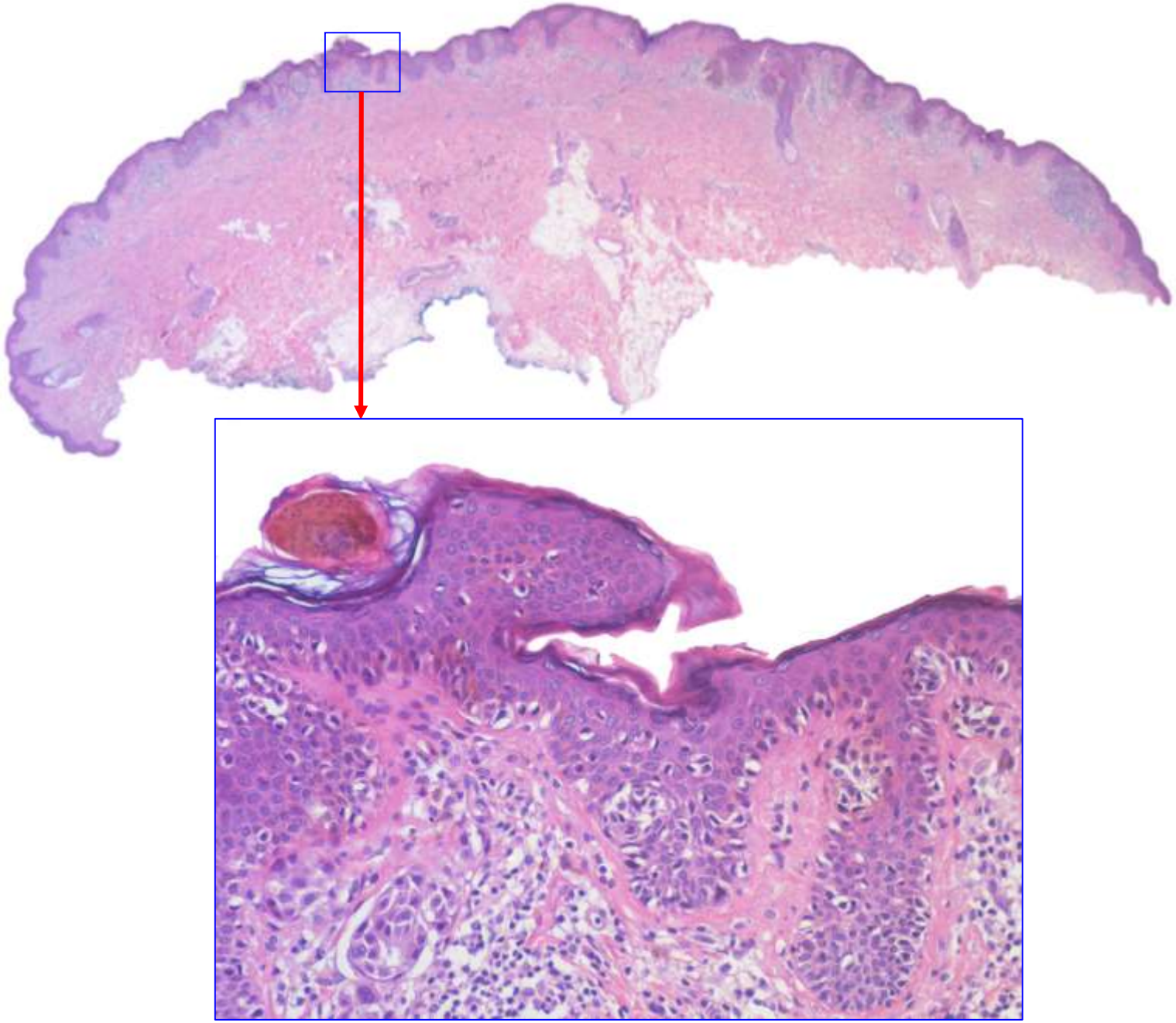
More is always possible, especially in melanoma with its genetic instability,



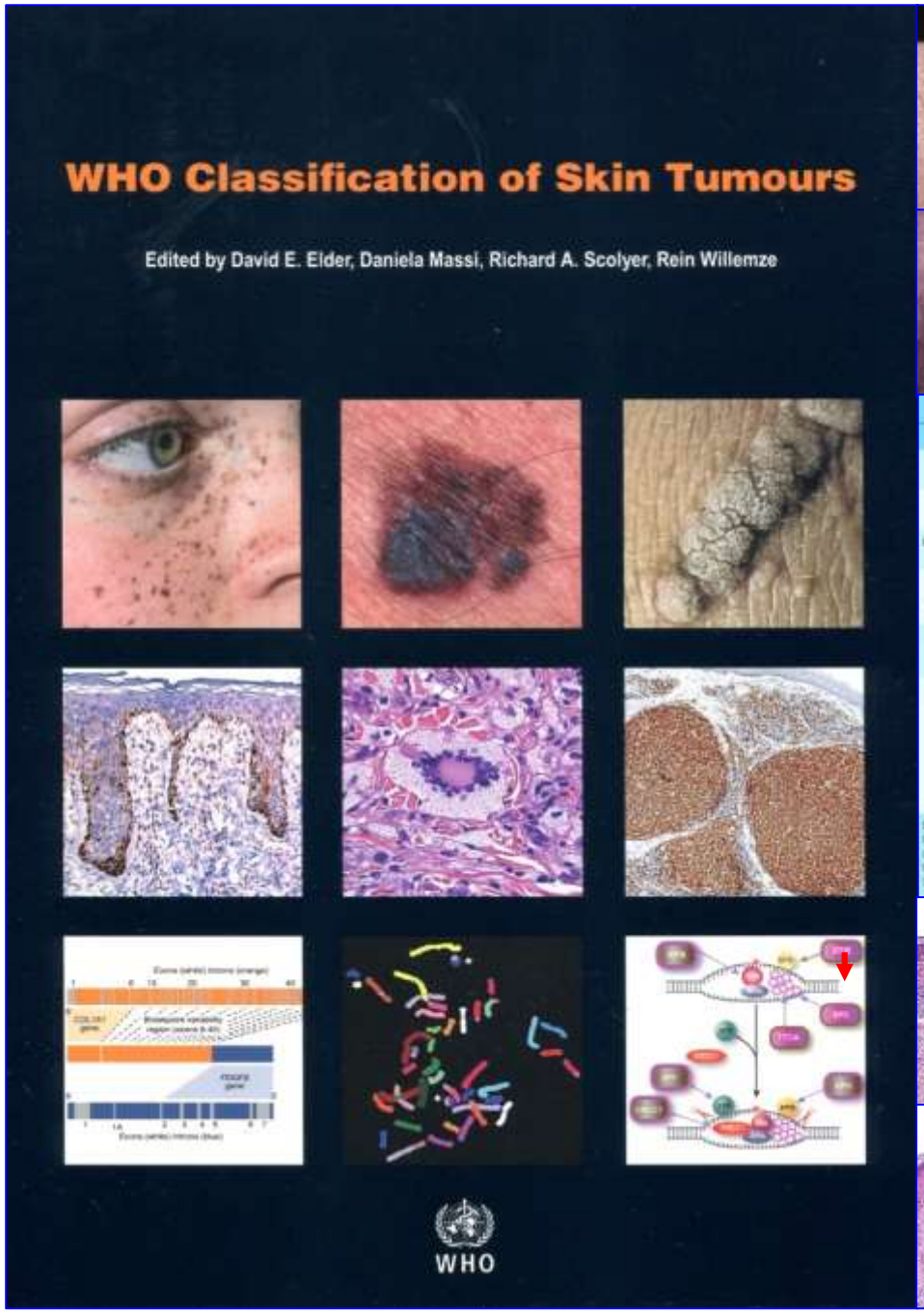
and in this sense, even these cells are not “fully transformed.”
If such terms are being used, they should be defined which has never been done. And if “fully transformed cells” are the measuring stick for malignancy,

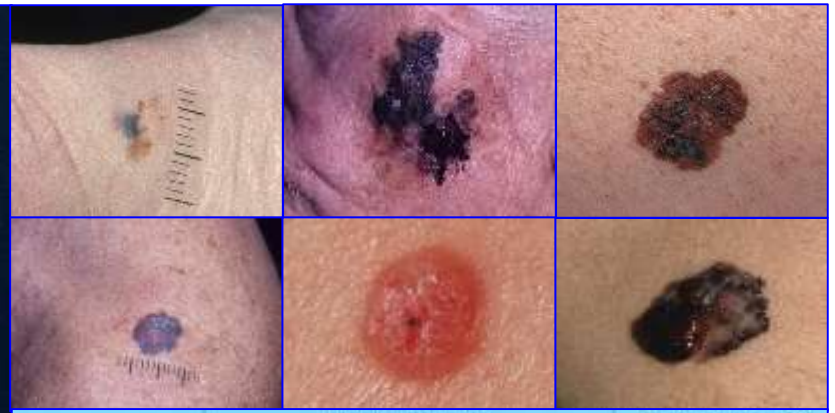


one cannot make the diagnosis of melanoma in cases such as this one. Then this lesion is not a melanoma



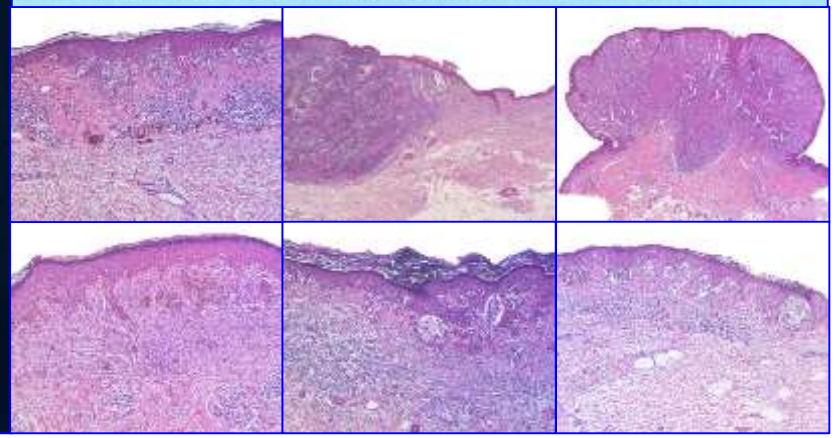
because its cells are only “partially transformed.” However, then one should not be surprised if, every now and then, patients without melanoma develop melanoma metastases.





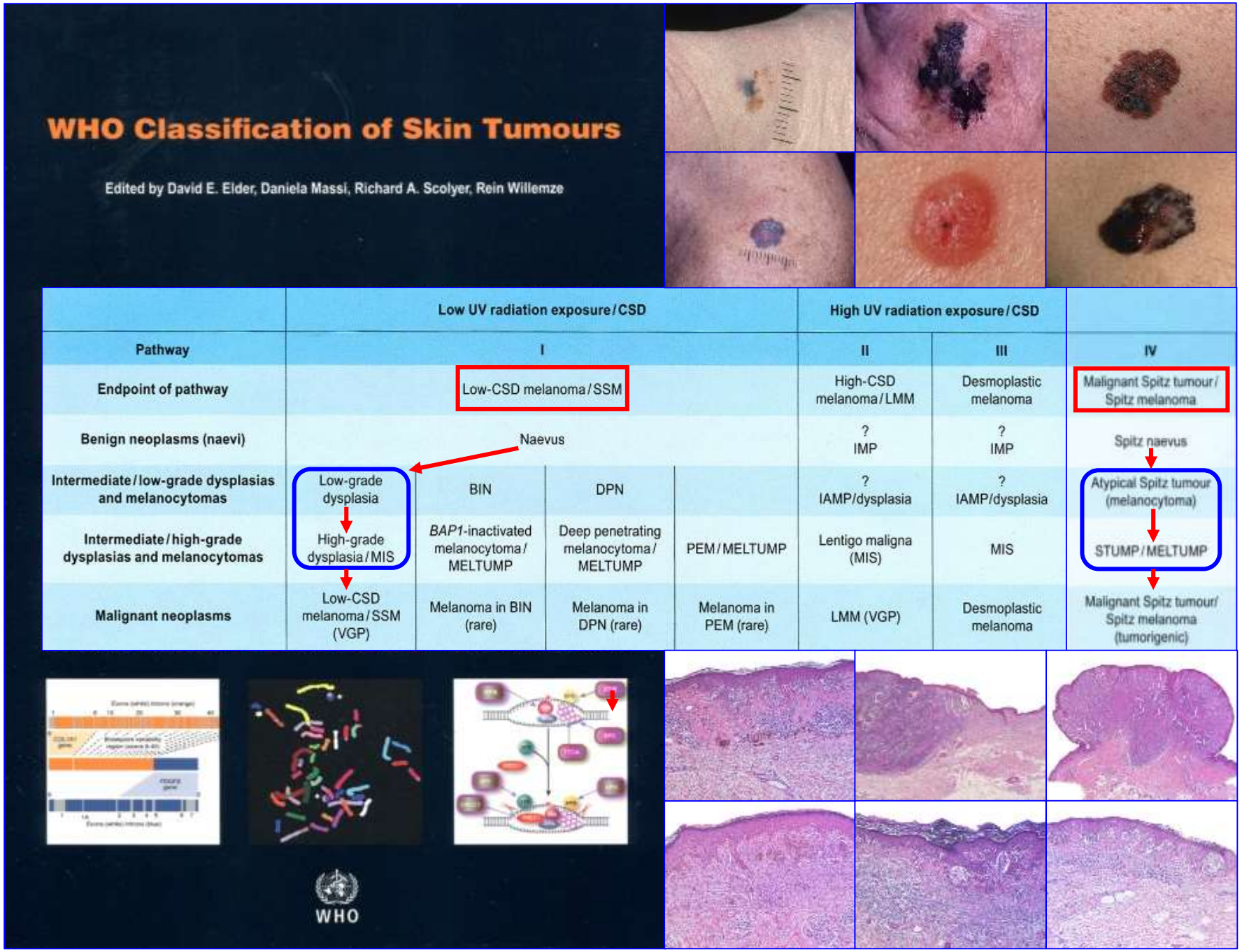
	Low UV radiation exposure/CSD				High UV radiation exposure/CSD	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma/SSM				High-CSD melanoma/LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate/low-grade dysplasias and melanocytomas	Low-grade dysplasia	BN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate/high-grade dysplasias and melanocytomas	High-grade dysplasia/MIS	BAP1-inactivated melanocytoma/ MELTUMP	Deep penetrating melanocytoma/ MELTUMP	PEM/MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma/SSM (VGP)	Melanoma in BN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[43]	***BRAF* p.V600E** or ***NRAS*** TERT, CDKN2A, TP53, PTEN	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF, MAP2K1*** or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS, BRAF*** (non-p.V600E), ***KIT***, or ***NF1*** TERT, CDKN2A, TP53, PTEN, RAC1	***NF1*** (PI3K, MAPK), MAPK1, BRAF, ESR1, MET TERT, NRAS, PIK3CA, PTPN11

BN, BAP1-inactivated naevus; **BN**, blue naevus; **CBN**, cellular blue naevus; **CN**, congenital naevus; **CSD**, cumulative sun damage; **DPN**, deep penetrating naevus; **IAMP**, intraepidermal atypical melanocytic proliferation; **IAMPUS**, intraepidermal atypical melanocytic proliferation of uncertain significance; **IMP**, intraepidermal melanocytic proliferation without atypia; **LMM**, lentigo maligna melanoma; low-/high-CSD melanoma, melanoma in skin with a low/high degree of cumulative sun damage; **MELTUMP**, melanocytic tumour of uncertain malignant potential; **MIS**, melanoma in situ; **PEM**, pigmented epithelioid melanocytoma; **SSM**, superficial spreading melanoma; **STUMP**, spitoid tumour of uncertain malignant potential; **UV**, ultraviolet; **VGP**, vertical growth phase (tumorigenic and/or mitogenic melanoma)

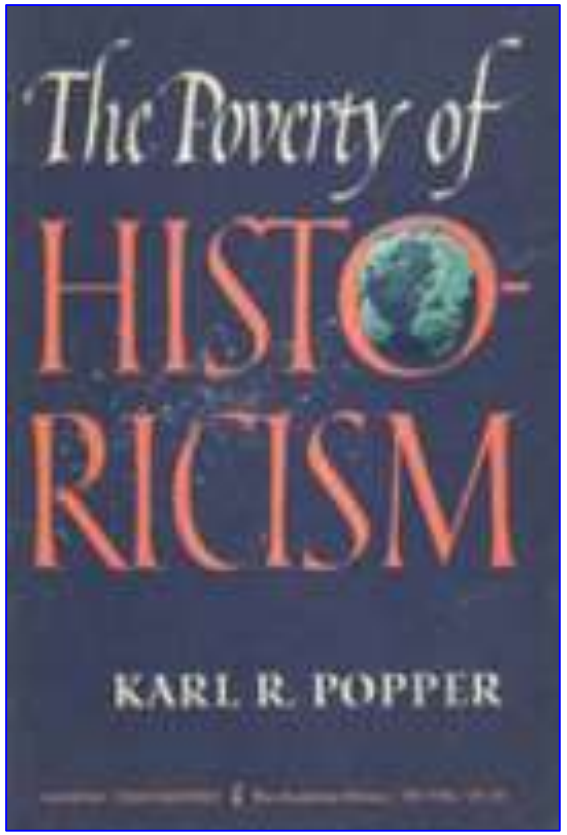


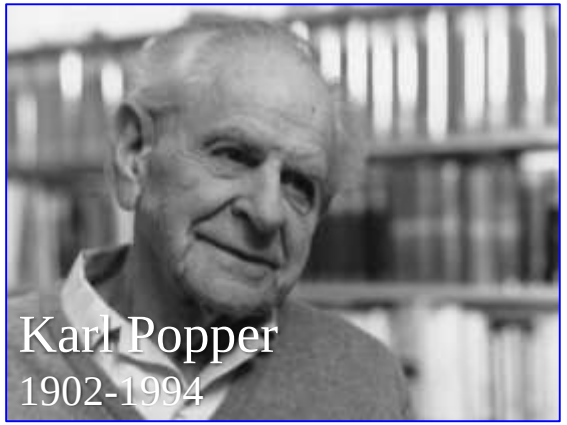
Classification is always difficult because no two individuals are the same.

As Buffon pointed out in 1745, *"the more one increases the number of one's divisions, in the case of products of nature, the closer one comes to the truth, since in reality individuals alone exist in nature."* Nevertheless, species can be distinguished in botany, zoology, and medicine, and possibly also in regard to melanoma.



Then, however, one must follow the genealogical evidence, unite different stages of the same process, such as melanoma in situ and invasive melanoma, distinguish different processes from one another, and refrain from inventing names for phenomena that cannot be categorized easily, such as so-called “dysplastic nevi” or “melanocytic tumors of unknown malignant potential,” and then change the meaning of those terms by reframing them as distinct biological categories.




Karl Popper
1902-1994

Methodological nominalists … hold that the task of science is only to describe how things behave and suggest that this is to be done by freely introducing new terms whenever necessary, or by re-defining old terms whenever convenient while cheerfully neglecting their original meaning. … Methodological essentialists are inclined to formulate scientific questions in such terms as 'what is matter' … and they believe that a penetrating answer to such questions, revealing the real or essential meaning of such terms and thereby the real or true nature of the essences denoted by them, is at least the necessary prerequisite of scientific research, if not its main task.

Karl Popper, 1957

Philosopher Karl Popper explained the difference between scientific attitudes as follows: *"Methodological nominalists … hold that the task of science is only to describe how things behave and suggest that this is to be done by freely introducing new terms whenever necessary, or by re-defining old terms whenever convenient while cheerfully neglecting their original meaning."* By contrast, *"methodological essentialists are inclined to formulate scientific questions in such terms as 'what is matter' … and they believe that a penetrating answer to such questions, revealing the real or essential meaning of such terms and thereby the real or true nature of the essences denoted by them, is at least the necessary prerequisite of scientific research, if not its main task."*

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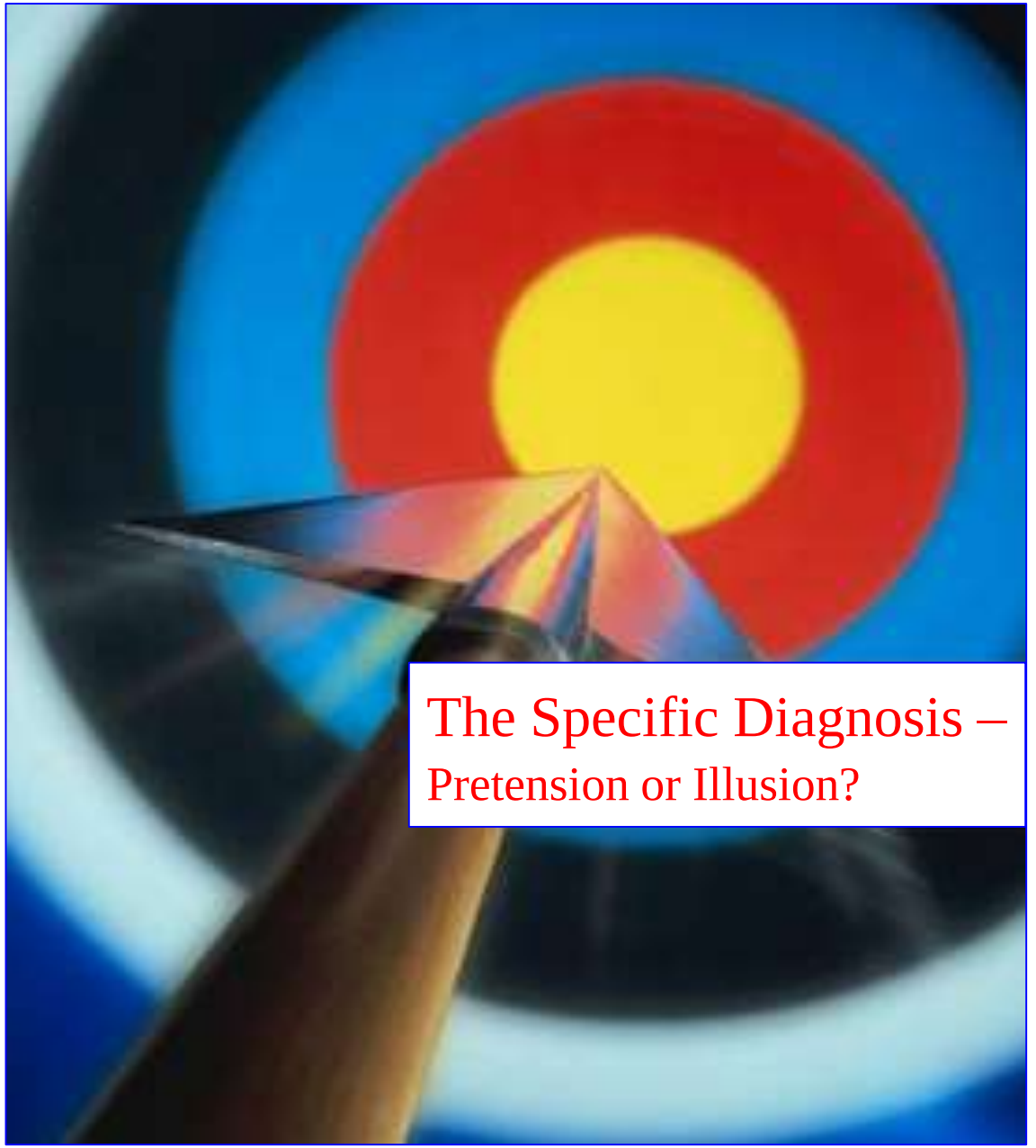
Karl Popper, 1957

Obviously, it depends on the scientific discipline whether recognition of species is the main task or merely a necessary prerequisite of scientific research. For many endavours, ranging from basic research to therapeutic trials, it is a necessary prerequisite, but for dermatopathology, as a diagnostic discipline, it is clearly the main task,



The Specific Diagnosis –
Pretension or Illusion?

and without rising to that challenge seriously, a specific diagnosis will remain an illusion.