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Agache's Measuring the Skin

Non-invasive Investigations, Physiology, Normal Constants

Second Edition

Springer

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Philippe Humbert • Ferial Fanian
Howard I. Maibach • Pierre Agache
Editors

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With 644 Figures and 157 Tables

Springer

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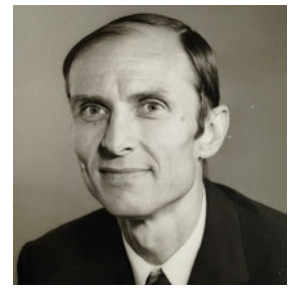

"This textbook is dedicated to the memory of its creator, Professor Pierre Agache, whose fingerprints are visible in every page".

Foreword

We live in a world of rapidly increasing information. The journalists and academicians often speak about this in a negative sense – utilizing the word "overload."

Many readers understand the overload phenomena and its impact on their daily life and work. Few of us can master the rapidly increasing data of the Information Age.

The Googles of the universe have aided us greatly in dealing with information overload.

It is divided into the pre- and post-computer age and has been expedited greatly by electronic searching and indexing. The Google world is attempting to ameliorate unmet need-indexing and electronic availability of the world's book collections.

In spite of all of these electronic advances and aids, we remain indebted to the rare scholar – in this case the late Pierre Agache – for his seminal contributions in the previous edition of this book.

Professor Agache was a dedicated, thoughtful, and disciplined scholar – making the previous edition one of the most valuable reference textbooks for anybody working in the dermatologic space, including the skin, hair, nails, and their other organ involvements.

This edition builds upon the work of Pierre's work.

We have in this edition – the current edition – a technology that Pierre did not have available.

The Springer organization has arranged so that this book will be updated – almost on a daily basis – when needed. The reader is now able to get updates in both electronic and print-on-demand versions.

We greatly appreciate the creativity and assistance of Dr. S. Klemp for making this available. We also thank the Springer team for their skilled assistance in their editorial process.

Your editors appreciate corrections and suggestions and can be readily reached by email and telephone.

Howard I. Maibach

Preface

Measuring the Skin: A New Look in Dermatology

Measuring the skin succeeds now to looking at the skin or inspecting the skin.

Many clinicians limited their diagnosis in dermatology on the only description of skin signs and skin lesions. The fundamental functions of the skin were not considered except through the aspect of the skin. For example, loss of barrier function was deducted of the dryness pattern of the skin. The development of cosmetology with new active ingredients which are enable to modify the skin physiology by targeting cell and their nucleus functions, has led the biometrologists to create the new instrumental devices to accurately assess the imperceptible modifications of the skin.

Since the skin is an organ which can be easily analyzed by looking, touching and smelling to evaluate some of its patterns such as roughness/smoothness, dryness/moisture, Stiffness/sagging, elasticity, extensibility, resistance, radiance/dullness, temperature and etc., it is now appreciated to be able to assess quantitative measurements, to visualize through the skin and inthe skin different structures such as dermis, vessels, appendages, etc.

The real development of methods to measure the skin took place during the 1970s. Indeed, in the last fifty years, the knowledge on the skin physiology and anatomy has been significantly developed in such a manner we are not able to imagine correctly the problems existed many years ago.

Up to these last years, histology remained the gold standard for morphological investigation of the skin, although biopsy may alter the original morphology. Advances in ultra-sound and optics provide nowadays a true in vivo analysis of the skin with precise and accurate signification, leading to the non-invasive optical biopsies. These progresses have many clinical applications in different fields of the medicine such as cancer diagnosis.

Thus a new semiology was born, requiring to be familiar with new patterns and signs. Healthy images at different anatomic sites as well as pathological data regularly appear in the field of biometrology, and need to be known by young researchers and dermatologists.

The data and images given by new technologies could be now available for the practitioners and physiologists which were reserved only to engineers and researchers in the past,. These methods give the possibility of repetitive histometric measurements of the same skin site.

Inflammatory diseases, blistering dermatosis and skin tumors are easily explored using new sophisticated methods, and the treatment effects can be evaluated. Since biometrology permits to follow the effects of such active principles, it is necessary to enter in the field of cutaneous pharmacology.

Another domain which interests the pharmacists, cosmeticians, doctors, researchers and also the people is skin aging. Indeed, skin appearance is changing with age, not only in terms of wrinkles and loss of elasticity, but also in terms of its moisture and radiance. Biometrological assessment allows to determine the mechanisms between intrinsic and extrinsic factors which are involved in skin aging process. The quality of the barrier function of the skin is assessed by numerous methods more and more sophisticated, allowing to have knowledges on the skin hydration in different levels. Further, new technologies such as RAMAN method helps to determine the qualitative and quantitative constitution of the skin; The non-invasive imaging technologies significantly improve the diagnosis and also clinical management of skin conditions while giving the dermatologist and closely related specialists, the new ways for assessing and exploring the skin in its unknown and invisible parts.

The aim of this new edition of Measuring the skin is to provide the doctor, the researcher, the cosmetician and all person who is involved in assessing the skin, with the tools and their usefulness to characterize the skin. In none of other field of medicine does such a book exist. Indeed, due to it superficial location and simple approach the skin is the target of every measure, every device, and all of its function have been explored. When written for the first time by Prof. Pierre Agache and myself in 2004, we didn't imagine at that time that a new edition will bring so many new information, and disclose so new fields of investigation.

This book has vocation to be the professional basic book of each of you, who wants to know how to characterize such skin property, and wants to know more on new skin physiology developments. In memory of my mentor, I am proud to follow him in this skin specialty he contributed to create and to develop.

Philippe Humbert

Acknowledgments

We would never have been able to finish this work without the help of our colleagues.

The authors would like to express their deepest gratitude to the persons listed below for their valuable help and support:

- Adeline Jeudy, Thomas Lihoreau, Sophie Mac-Mary, Jean-marie Sainthillier, Alexandre Guichard and Ahmed Elkhyat for their help to update the table of contents and the new authors according to the recent publications.
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- Deep thanks to the Springer team who followed the redaction process patiently and efficiently.
- In memory of Pr. Xuemin Wang, Vice-Chairman of Shanghai Skin Disease Hospital, who has written two wonderful chapters on microbiology of the skin in this edition. Unfortunately he expired on February 2016 without having the opportunity to see the outcome.
- Special thanks to Mr. Emmanuel Leclerc, editorial director and Mrs. Sylvie Cortes, Edition Department assistant at « Lavoisier » editing house in Paris who dedicated the all legal autorisations to Springer for the upcoming edition of this textbook.
- Finally a no-name appreciation to all secretaries, colleagues, collaborators and medical and university staffs who helped the authors/co-authors during this long project.

Phillippe Humbert
Ferial Fanian
Howard I. Maibach

Introduction

Ferial Fanian

Readers of the previous edition of this book have relied on it to aid them in measuring all parameters of the skin through the appreciable work of Pierre Agache and Philippe Humbert. After the heart-rending death of Pierre Agache in 2003, the first edition was published on 2004 by Springer which was a modified complete translation of the french version edited by him and published in 2000 by Lavoisier (Physiologie de la peau et explorations fonctionnelles cutanées).

Unfortunately the second version was delayed according to several administrative reasons till I have been asked on 2011 to start this big project. Although it was a noticeable major job, it was my great honnor to work with the well known authors and also the two great editors, Howard Maibach and Philippe Humbert who always made me the fruitful suggestions and were my enthusiastic supporter through out this long project.

I would like to appreciate all of the respected authors and editors and also all of my friends and colleagues which are named in acknowledgment.

I would like to express my special thanks to Doctor Aude Agache, the esteemed daughter of Professor Agache who did kindly help the team to carry out all administrative steps successfully.

At the end, I would like to dedicate this work to my mother and father, Saeideh Bashirazami and Mohamadali Fanian, which are my first and permanent encouraging teachers to study more and more, to my dear Professors, Yahya Dowlati and Alireza Firooz who gave me the scientific view and motivated me always to go on even in the hard moments, and finally to my husband, Massoud Salari, who was always at my side cheering me up and supporting me through the happy and unhappy moments and also my son, Sepanta Salari, who understood patiently my busy time during this hard project.

Procedure

The table of the contents was modified in order to add the most updated technologies in skin physiology, biometrologie, biophysics, imaging and clinical scoring. The authors have been selected according to the most recent published articles in each field.

Comparing to the first edition with 84 chapters and 784 pages, this new edition contain 160 chapters and 1652 pages which can cover the most of the researchers' needs in this domain.

Fortunately, this volume has been selected to become part of the SpringerReference portfolio, which now comprises over 400 major reference works and almost 500,000 entries/chapters online. This means it will not only be a static printed book, but it will have a "living" update version online which is very important for this book because of its gadget like nature.

Contents

In the first section, we have considered an anatomic approach for the chapter titles : you will start with the surface of the skin and then you will go deeper by leafing the pages. Then you would discover the different measuring techniques according to the functional approach : Mechanical, Photoprotection and sensory function of the skin. Furtherly, you will find the standard scoring scales (which will be more completed for the next edition) and the book finishes with skin maps.

We have kept most of the precious chapters of Pierre Agache whose scientific value still remain intact even after 10 years.

All of the reader's precious comments are welcome.

On behalf of the editors, I would like to invite all of the researchers who are interested to introduce the new methods in the global domain of "Measuring the Skin", to contact the editors.

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About the Editors

Philippe Humbert
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Professor Humbert has been elevated to the grade of Professor of University in 1993, at the age of 34 years. Specialist in Dermatology as well in internal Medicine, Allergology and clinical Immunology, and skin oncology, he performed a Ph.D. in cutaneous Pharmacology.

During his position of head of the Department of Dermatology in the University Hospital of Besançon from 1993 to 2015, he developed a clinical department with all the specialties of Dermatology, i.e., Allergology, Surgery, Laser, Internal Medicine, Oncology, pediatric Dermatology, Photobiology, Biometrology.

During the same period, he created the Laboratory of Cutaneous Biology in which news skin models are developed as well as cell cultures (keratinocytes, fibroblasts, melanocytes. . .) which are used as pharmacological models.

On a clinical point of view, he created the CERT (Center for Investigation and Research on the Skin) in which, with a team of engineers, doctors, pharmacists, technicians, he performss clinical studies for evaluation of cosmetics or drugs.

In this field of biometrology, he was elected as President of the ISBS (International Society for Bioengineering and Imaging of the Skin) from 2005 to 2010 (he organized indeed the International Meeting of ISBS in Besançon in 2009), as well as President of the International Society of Cutaneous Pharmacology. He was President of ESCAD in 2011.

His bibliography includes more than 350 publications and five books.

Professor Philippe Humbert received the Award of the French Society of Dermatology, of the French Society of Dermatological Research, as well the French Society of Cosmetology.

Known for his humanism and generosity, Professor Philippe Humbert welcomes many students or professors coming from abroad, and he was proud to contribute to teach six famous Chinese Professors. He collaborates with many universities over the world. Believing in the creativity of his students, he helped them to assess three innovative start ups in the domain of skin biometrology (Skinexigence^{R}), skin biology (Bioexigence^{R}), and skin pharmacology (Proviskin^{R}).

Student of Pr Agache, his Editor position is the way to honor his mentor, and to contribute to his artwork.

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Ferial Fanian is a French-Persian dermatologist working in Research Centre of Department of Dermatology of Besançon, France (CERT). She has a remarkable experience on laser applications in dermatology while she was always working as a researcher in biometrology of the skin.

She is also familiar with optical Biopsy methods particularly with in vivo Confocal Microscopy and that is why she is the board member of ICNI group (Non-Invasive Cutaneous Imaging thematique Group) at French Society of Dermatology. She was working on melanocytes activity and morphology through her PhD thesis. She has also obtained two academic fellowship in « Laser and Cosmetic Dermatology » and also « Innovative Chronic Wound Healing » in 2012 and 2013 in France.

Actually, she is the reviewer or invited author for several English and French scientific journals in the field of dermatyology, aesthetic medicine and biometrology such as JEADV, Archives of Dermatology, Journal of Cosmetic Dermatology, Case Reports in Dermatological Medicine, Medical Staff Dermatologie, Réalités Thérapeutiques en Dermato-Vénérologie.

Research Interests
Advances and Emerging Techniques in Dermatology
Anti-Aging
Cosmetic Dermatology
Invasive and Non-Invasive Methods in Dermatology
Investigative Dermatology

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Present Title: Professor

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Tulane University, New Orleans, LA	M.D.
USPHS, Hospital of the University of Pennsylvania	Resident/Fellow

HONORARY DEGREES	DEGREE	YEAR
L'Universite de Paris-Sud, France	Ph.D.	1985
Université Claude Bernard Lyon 1, France	Ph.D.	2008
University of Southern Denmark	M.D.	2010

Dr. Howard Maibach joined the University of California Faculty in 1961 as Assistant Professor, and is currently Professor of Dermatology.

Dr. Maibach, an expert in contact and occupational dermatitis, sees patients at the Environmental Dermatoses Clinic, which is part of the Dermatology Clinic at UCSF. His most active fields of research are dermatopharmacology, dermatotoxicology, and environmental dermatoses. He has been doing human subject research for 45 years.

He has been on the editorial board of more than 30 scientific journals. His bibliography includes more than 2790 publications and 100 books.

He is member of 19 professional societies, including the American Academy of Dermatology (AAD), San Francisco Dermatological Society (SFDS), North American Contact Dermatitis Group (NACDG), American Contact Dermatitis Society (ACDS), International Contact Dermatitis Research Group (ICDRG), Society of Toxicology (SOT), European Environmental and Contact Dermatitis Research Group (EECDRG), and the Internal Commission on Occupational Health. He is a consultant to government, academia, and industry worldwide.

Dr. Howard Maibach was honored as the 2013 recipient of The Master Dermatologist Award by The American Academy of Dermatology's 71st Annual Conference held in Miami, Florida. This prestigious award recognizes an Academy member's significant contributions to the field of dermatology and to the American Academy of Dermatology.

In March 2015, The International League of Dermatological Societies (ILDS) awarded Dr. Maibach their 2014 ILDS Certificate of Appreciation in recognition of his outstanding contribution to dermatology, both nationally and internationally, through his work, research, publications, and teaching in the USA and over 60 countries.

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The Human Skin: An Overview

1

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1 A Few Figures About the Skin

Area: 1.8 m^2
Average thickness: 1.2 mm
Average volume: 3.5 dm^3 = 0.035 m^3
Weight with blood: 4.7 kg
Weight without blood: 4.2 kg
Ratio area/thickness = 150,000

The skin participates in many physiological and pathological events and processes of the human organism, owing to its large area of contact with the internal milieu, but also to its volume and variety of tissues. The cutaneous expression of internal diseases is frequent, varied, and often specific.

2 Skin Structure

The general structure of the skin is a stratified tissue whose four layers are, from the top to the bottom, the stratum corneum (8–20 µm thick, could go up to 1.5 mm on palms and soles), the viable epidermis (30–80 µm), the dermis (1–2 mm), and the hypodermis or subcutis (0.1 to several cm) (Fig. 1). Each of these layers has its own physiology, functions, and evolution along life.

2.1 Annexes

The skin is a heterogeneous organ (dead tissue, epithelium, connective tissue, muscles, etc.), and furthermore it harbors four types of independent mini-organs, also called skin appendages:

– The nails, growing at a speed of 3 mm/month on hands and 1–1.5 mm/month on feet, with this speed decreasing with age (Scher and Daniel 2007)
– The pilosebaceous follicles and hair: between 90,000 and 130,000 on the scalp, with a terminal hair diameter of 40–120 µm, depending of the phototype; 60–100 hair fall per day, and they grow at a speed of 0.35–0.44 mm/day, (1 cm/month, 12 cm/year) (Blume-Peytavi 2008; Guichard et al. 2013)
– The eccrine sweat glands (three millions)
– The apocrine sweat glands (armpit, perineum)

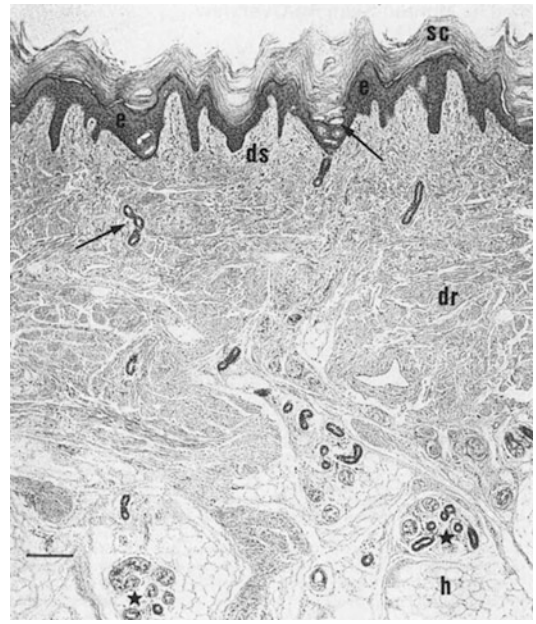

Fig. 1 A vertical section of the plantar skin. *dr* reticular dermis. *ds* superficial dermis. *e* viable epidermis, *h* hypodermis and adipose tissue, *sc* stratum corneum. *Stars* coiled part of sweat glands (both secretory segment and lower duct). *Arrows* sweat ducts. Note the large skin thickness (1.8 mm, in other sites it would be close to 1 mm), the absence of pilosebaceous follicles, the large thickness of the stratum corneum, and the great number of sweat glands. In vivo dimensions were about 15 % larger. Bar = 200 µm (From Degos and Civatte 1977)

2.2 Variations

Topographical variations in its structure and functions are considerable: the scalp, the skin of the face, the dorsal skin of the hands and feet, the

palms and soles, the armpits, and the perineum have their own anatomy, functions, and reactivity (Tagami 2008; Sandby-Møller et al. 2003; Waller and Maibach 2006).

To briefly give some examples, in usual temperature and hygrometric atmosphere conditions (20–22 °C, 40–60 %), skin sebum excretion could vary from 0 (arms, legs, etc.) to more than 200 μg/cm^2 (greasy subjects forehead), and hydration index could go from 10 (dry skin on the legs) to 100 (well-hydrated skin on the forehead, without unity).

Aging (intrinsic or extrinsic) is obviously modifying skin structure (Lévêque and Agache 1993):

- Hydration presents maximum values between 20 and 40 and then regresses.
- Elasticity is the mechanical property that better reflects skin aging: it decreases and becomes oriented with age, is sun exposure dependent, and more important on women, and its values decrease from head to feet.
- Skin microrelief, roughness, and wrinkles are not involving on the whole body in the same manner, again depending on topology (gravity, expressions, etc.) or environmental factors (sun, tobacco, etc.), along life (Guinot et al. 2006);
- Microcirculation: capillary density, structured at the beginning even if variable in density in different body areas (mean of 60–70/mm^2), could worse until a disorganized (orientation), heterogeneous (size, shape of the capillaries) network, characterized by a density of 30/mm^2 or less.

The skin characteristics are also function of **sex** and **ethnicity** of the subject; it could even be dependent on the **side of the face** (Mac-Mary et al. 2010) or **environmental factors** (season, weather, etc.) (Fanian et al. 2013).

Due to these important variations, parameters previously cited appear in publications in comparison before and after a treatment, rather than compared to "normal" or "pathologic" values.

3 Skin Functions

3.1 Specific

- Self-maintenance and self-repair (but there is no repair of appendages)
- Mechanical protection: resistance to frontal and tangential shocks, attenuation of external pressures, body external shape maintenance through reversible deformations, adhesion of the palms and soles to objects in the hand and on the ground
- Chemical barrier: limitation of foreign substances penetration, prevention of water and endogenous fluid loss
- Protection against ultraviolet rays
- Protection against environmental pathogenic microorganisms
- Social and psychological function through the physical aspect and mimic

3.2 Exerted in Cooperation with Other Organs

- Sensory function: tactile senses, perception of temperature and pain and even of light (popliteal region) (Campbell and Murphy 1998)
- Body temperature control: especially regulation of heat gains and losses
- Immune function: the skin is the first line of information and defense in the process of immunity, especially "delayed immunity"
- Ossification: synthesis of provitamin D (vitamin D is responsible for the intestinal absorption of calcium)
- Sexual function: conversion of testosterone into more active dihydrotestosterone

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Measurements of the Human Skin: Why and How?

2

Pierre Agache

Contents

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In experimental sciences, measuring phenomena is a key point, since it is through the quantitative evaluation of an effect related to a given cause that the law of phenomena can be founded. (Bernard 1984)

1 The Relevance of Measurements

Metrology is the science of measurement, of evaluation of its requirements, limitations, and interpretations. The primary reason for using metrology in cutaneous noninvasive investigations is its role as a major source of progress, not only because impressions are replaced by objective facts and qualitative descriptions by quantitative assessments, but also because new situations are unveiled. Even the simplest phenomenon becomes complex when measured; one starts from one fact and then discovers its possible components and variations, which induces new hypotheses and opens a pathway for new knowledge. Physics in the past could only progress through the development of measurement methods. The remarkable advances in human physiology during the nineteenth century, which preceded modern medicine and allowed it to progress, came about because of a double process of discovery and quantification. Skin metrology provides many examples. The measurement of sebum secretion with a view to correcting the removal of lipid from the surface quickly showed that the measured phenomenon was not the one expected, but rather the partial emptying of a follicular reservoir, the existence of which had previously been ignored. The measurement of epidermal turnover in psoriasis provided a leap forward in understanding the disease.

Biological phenomena are changeable and difficult to quantify. At first glance, observation may prevail over measurement, but the notion of dimension is required to investigate a structure and the magnitude of change. The pathologist must decide whether, in the visualized skin section, the tissue components are modified in dimension and number by a pathological process. Furthermore, normal characteristics vary depending on the anatomical site, which has not yet been quantified; consequently, the pathologist remains unable to reach a conclusion unless major changes are seen. When the noninvasive anatomical or functional investigations are quantitative, they provide a measure with low subjectivity. The clinician evaluating a new medication would like to rapidly and accurately assess treatment efficacy; this goal can be reached only by quantification of clinical symptoms. Accordingly, it is necessary to know whether the measure is accurate (degree of precision and variability) and if it truly reflects the targeted phenomenon.

Numerical results of blood sample examinations is standard practice. It is likely to be the same for most clinical symptoms in the years to come. This is possible today in the detection and substantiation of subtle changes (e.g., aging (Escoffier et al. 1989; Larnier et al. 1994)) or the effect of a therapy on a chronic disease such as scleroderma (Humbert et al. 1993). The last decade of progress in molecular genetics has emphasized the considerable benefit that the collection of data provided by everyday medical practice might generate, and in years to come practitioners will certainly be involved in collecting and processing this data. Such information requires classification, substantiation, and treatment using statistical parameters. A few nondermatological specialties also utilize skin measurements, e.g., in physiology (endocrinology, body temperature regulation, immunology, etc.), where the skin is an effector organ readily examined noninvasively because of its accessibility. It is also the case for cosmetology research, where innocuousness and efficacy criteria may become visually unattainable because of their subtlety, and require instrumental measurements for assessment.

2 Types of Measurements

Before choosing an appropriate evaluation method, it is necessary to look at the nature of the data. If they relate to individuals or categories, hence with no possibility of converting them into numbers, the evaluation mandates a nominal scale. If the data can be translated into numbers, but on a scale where intervals are unknown or uneven, they can only be ranked. Finally, if the variation is measured on a continuous scale with even intervals, then the traditional evaluation is used: the so-called parametric evaluation (Siegel 1956).

2.1 Nominal Scale

This is the only means of measuring categories, facts or states, named by a word or an expression, and not put into numbers, for example, aggravation, desquamation, over 60-year-old subjects, etc. The nominal scale uses a number or the percentage of a total. If the measured category is part of a series, it can be replaced by a number for easier presentation, but without ranking.

A percentage should be presented with its uncertainty margins, thus its standard deviation (SD). The latter is calculated by the formula $SD = [p(1 - p)/n]^{1/2}$, where p is the percentage (from 0 to 1) and n the total number of data. The confidence interval for an occurrence by chance of less than 5 % is that between two standard deviations on each side of p. Tables of 5 % confidence intervals can be found in statistics textbooks. A close evaluation can be obtained using an abacus (Fig. 1).

2.2 Ordinal Scale

The ordinal scale provides only a ranking. This type of scale should be selected for two reasons: either the data are part of a discontinuous series, thus one cannot apply a number to them, or they come from a continuous series, but on an unknown scale on which it is not known if the distances between the measured objects are equal or proportional: only the rank is identified. For instance, nonexistent, slight, good, and very good improvements can be rated 0, 1, 2, 3, knowing that 3 does not mean that the improvement was 3 times better than 1. To describe series of this type, the adequate parameters are the median and the extreme values. Graduated scales should be avoided (especially when the series is made up of averages) because they may be mistakenly used for parametric measurements instead of being more accurately applied to ranking measurements. This type of classification is particularly indicated in psychosensorial evaluations in which the phenomenon under study varies discontinuously, or continuously but with unknown intervals.

2.3 Interval Scale

Interval scales are most commonly used in evaluation for numbers in a continuous series. Units may be changed if the scale is the same (e.g., temperature in the same series can be converted from Celsius into Fahrenheit degrees and vice versa). If the data have a gaussian (or normal) distribution, they can be described by the mean and its standard error (i.e., the standard deviation of the mean); otherwise the adequate parameters are the median and the extreme values. If it is previously known that the studied parameter has a gaussian distribution, one can surmise that the means of samples equal to or greater than 30 are also normally distributed. In a comparative evaluation, it is often possible that each subject is its own reference; this avoids the interindividual source of variation (important in biology) and makes it possible to use statistical tests for matched pairs.

2.3.1 Opposition Method

The opposition method, also called the zero method, is used to obtain a higher degree of precision than a direct measurement. The rationale is to measure only the difference between the unknown quantity and another very close and already precisely known value. The measure of

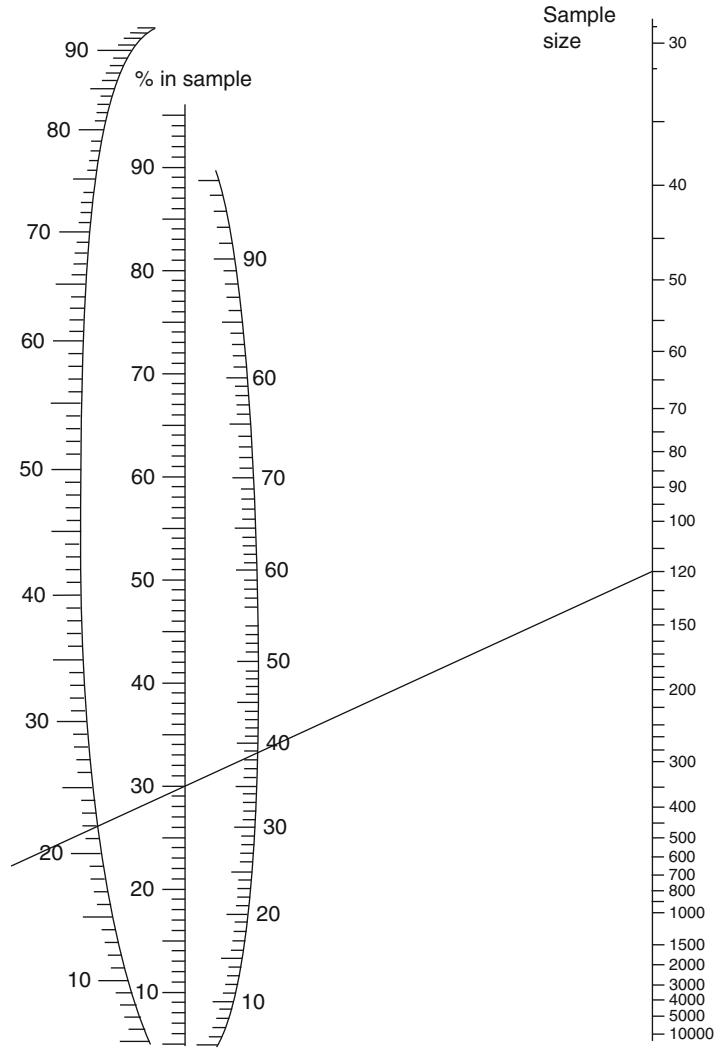

Fig. 1 Confidence interval of a percentage when the probability of a greater or lower number occurring by chance only is limited to 5 %. As shown, if the sample size is 120, the 5 % confidence interval of 30 % is 22–39 %. If the sample size is 40, the 5 % confidence interval of 30 % is 18–47 %

the difference can be more precise because it deals with a much smaller quantity. Consequently its precision, related to the initial value to be measured, becomes more accurate. For instance, to weigh sebum laid on a glass slide, the slide is placed on one pan of a pair of scales and a standard mass of a similar weight known with great precision (e.g., a glass slide without sebum) is placed on the other. Then a weight is added on the lighter side to make up the difference and this difference is then measured. The International Bureau of Weights and Measures has scales designed for this type of differential weighing.

2.3.2 Psychosensorial Evaluations

For the psychosensorial evaluations in which the studied phenomenon is believed to vary in a continuous and uniform way (equal intervals), a nongraduated linear scale is used for each measurement. Generally this measurement consists of a 10-cm-long horizontal line, with zero on the left end and ten on the right; the measurement is indicated by a small vertical stroke. Graduated scales are less suitable because they tend to distort the scoring by favoring values close to the graduations, with the operator influenced by the value indicated. However, operators should be well

aware of the scale extremes (zero and ten), which sets the limits of the measure; consequently its variability is lessened. Another way to decrease variability is to replace the absolute measurement by a comparative measurement: the objects to be compared are placed next to each other so that they are perceived almost simultaneously; the nearer they are in time and space, the more accurate the measurement is. Operator training is also important.

3 Selecting the Suitable Unit

The units can be either arbitrary (e.g., millimeters on the linear scales used for psychosensorial measures), or arbitrarily linked to international physical units (e.g., skin blood flow measured in volts by the Doppler), or absolute (e.g., skin blood flow measured by the epicutaneous xenon clearance in milliliters per minute per 100 g soft tissue). Physical units are always better than arbitrary units, and absolute units are preferred to those of other associated physical phenomena (e.g., measuring stratum corneum water depletion in milliliters per square centimeter per hour, as compared to decreased electrical impedance). Creating dermatological or biological units should be avoided when it is possible to use internationally approved units so that skin structure and properties remain within the physics of all other materials for easier comparison and the opportunity to use the laws of physics and chemistry for interpretation, thus considerably increasing the benefit of the measurements, also necessary for scientific progress.

We recommend measurements in units of the *Système International d'Unités* (SI), also called the MKSA system, the four fundamental units of which are the meter (m), the kilogram (kg), the second (s) and the ampere (A). Skin area is commonly measured in square centimeters, its thickness in millimeters, etc. For the derived units, the conversion between the centimeter-gram-second (CGS) system, MKSA, or other systems is often a source of error. See conversion tables in ▶ Chap. 160, "Correspondence Between International System Units (MKSA) and CGS Units."

4 Data Presentation

Faced with a variation or a distribution, the first step to prepare is a graphic representation: a curve or a histogram. The eye appreciates at once a series of features necessary for the interpretation and the processing of the information, for example, the gaussian or nongaussian characteristic of a distribution, the linear or nonlinear character of a relation, and the absolute level of a measure. Misunderstandings often stem from skipping this step.

When studying a histogram, the first question is "Does it fit a well-known distribution?" because the processing and interpretation of the data is then easier. A gaussian distribution, bell-shaped and symmetrical, means that data are independent of each other and that the distribution most probably results only from their summation. A distribution with two peaks may correspond to two interpenetrated gaussian curves. To rapidly check if a distribution is gaussian, the use of gaussometric graph paper (or gaussologarithmic if the abscissa is in logarithms) is suitable: it provides a quick calculation of the adjustment to this type of distribution. An asymmetrical histogram may indicate a binomial distribution. A substantial asymmetry suggests a Poisson distribution (a particular case of binomial distribution). An asymmetrical distribution can sometimes be transformed into a gaussian one by using the logarithm of the data.

Showing a variation through a mathematical function (of time or any other parameter) indicates major progress in data interpretation, if the variable has an anatomical or functional meaning. This makes it possible to use the function in other situations, sometimes to generalize its use, with further progress in knowledge. However, a purely descriptive mathematical model (i.e., when variables are devoid of biological meaning) is of minimal interest. The linear function speaks for itself and is one of the most profitable functions through the calculation of the slope and intercepts with the axes. It can be deduced from an exponential function by taking the logarithm of the data, and from any other function by replacing x on the x-axis with a power of x (e.g., for $y = a + b/x$, $1/x$ is put on the x-axis).

5 Precision of Measures

In a common parametric measurement, the highest level of accuracy is desirable, even if ultimately the decimals are rounded for convenience. Only the significant figures must be mentioned. Sampling uncertainty should always be mentioned, together with the observed variation.

5.1 Calculation of the Maximum Experimental Error in Measurements

To predict the maximum possible error in a measure of combined quantities from the separate measure of each quantity, the standard rules are:

- The absolute error Δy on a sum $y = u + v$ is the sum of the errors on each component $\Delta y = \Delta u + \Delta v$.
- The absolute error Δy on a difference $y = u - v$ is the sum of the errors on each component $\Delta y = \Delta u + \Delta v$.
- The absolute error Δy on a product $y = uv$ corresponds to the formula $\Delta y = u\Delta v + v\Delta u$. The relative error $\Delta y/y = \Delta u/u + \Delta v/v$.
- The absolute error Δy on a quotient $y = u/v$ corresponds to the formula $\Delta y = (u\Delta v + v\Delta u)/v^2$. The relative error $\Delta y/y = \Delta u/u + \Delta v/v$.

Note that these errors (Δu, Δv, etc.) are experimental errors on crude data and have no relation to statistical errors which are dealt with in the following paragraphs.

5.2 Variation in a Gaussian Distribution

In a gaussian distribution, the mean (m) must be presented with its uncertainty limits (i.e., either standard deviation and number of data, or standard error of the mean). The standard deviation (SD) must be mentioned with the number of observations (n) because the confidence interval it indicates (95 % confidence interval ranges between two standard deviations on each side of m) differs with the number of measurements. The standard error could either be mentioned (SD divided by the square root of the number of observations), as in the error bars of a graph of means. If the data are logarithmic, the mean must be geometrical (n^{th} root of the product of n data). In the case of a percentage, both the SD and the number of data should be mentioned.

5.3 Variation in an Atypical Distribution

If the histogram does not show a gaussian distribution, it should be described using the median instead of the mean, i.e., the value under and above which 50 % of the observations are found. The variability around this value is indicated in the quartiles, which are the values under which 25 %, 50 %, and 75 % of the observations are made. One can also mention the centiles (or percentiles), the 80th centile being the value under which 80 % of the data are found.

The constant search for precision must not be sterilizing. An isolated mean, a separate percentage, a graph with no mention of variation are only indicators, but are always preferable to the text alone.

6 Comparative Measurements

One purpose of a measurement is to compare the obtained value to others, to ascertain whether the observed difference is true, or rather to calculate the probability that it might originate from chance alone. The methods chosen vary according to the type of measurement.

6.1 Comparison of an Isolated Value (x) to a Gaussian Series of More than 30 Numbers

Its distance to the mean of the series determines the probability for the value x to belong to this reference population by chance alone. For a

distance of 1 SD, the probability is 15.9 %, for two SDs 2.3 %, and for three SDs 0.13 %. The exact probability is the total area (=1) under the Gauss curve minus the part of that area beyond x on the x-axis. It can be found in gaussian curve tables, where it has to be divided by 2 since the value of x is located on one side of the mean (one-tailed test).

6.2 Comparisons of Two Series of Measurements

6.2.1 Gaussian Series or Series Larger than 30

Use the test of comparison of variances (statistics manuals: F tables), followed by the usual parametric tests of comparison of means.

Series with Variances (s^2) Not Significantly Different

– Independent samples n_a and n_b are ≥ 30; use the formula:

$$\in = (m_a - m_b)/\left({s_a}^2/n_a + {s_b}^2/n_b\right)^{0,5}$$
$$\text{with degree of freedom } (df) = n_a + n_b - 2$$

– Independent samples n_a and n_b are <30; use the formula:

$$t = \frac{m_a - m_b}{\sqrt{\left(\frac{1}{n_a} + \frac{1}{n_b}\right)\frac{s_a^2(n_a - 1) + s_b^2(n_b - 1)}{n_a + n_b - 2}}}$$
$$\text{with } df = n_a + n_b - 2$$

– Matched samples: the calculation is made on the paired differences (n pairs): use the formula:

$$t \ (\text{or} \in) = m.n^{0.5}/s, \ \text{where}$$
$$df = n - 1 \ \text{and}$$
$$m = \text{the mean of differences.}$$

The parameter (distance to the mean, calculated in standard deviation) is the same for the three situations, but it is called $\in$ or t depending on the size of each sample (30 or <30, respectively).

Series with Significantly Different Variances (s^2)

The same formulas are used but the number of degrees of freedom used to refer to the probability table must be modified according to the formula of Welch's G test,

$$\frac{1}{ddl} = \frac{1}{n_a - 1}\left[\frac{s_a^2}{n_a s^2}\right] + \frac{1}{n_b - 1}\left[\frac{s_b^2}{n_b s^2}\right]$$

the global variance s^2, calculated by the equation: $s^2 = {s^2}_a/n_a + {s^2}_b/n_b$

The threshold value of parameter t depends on the risk α and the one-tailed or two-tailed character of the hypothesis to be checked.

6.2.2 Nongaussian Series

Nonparametric tests should be used, for example:

– Comparison of two nominal-type series: χ^2 test
– Comparison of two independent ordinal-type series: Mann and Whitney test
– Comparison of two matched ordinal-type series: Wilcoxon's matched pairs signed-ranks tests
– Comparison of two independent interval-type series: randomization test for two independent samples (Siegel 1956)
– Comparison of two matched interval-type series: randomization test for matched pairs (Siegel 1956) (the most powerful nonparametric test)

6.3 Simultaneous Comparison of Several Sets of Measurements

- Gaussian series: one-way variance analysis (ANOVA)
- Nongaussian series:
  – Nominal type series: #χ^2 test
  – Independent ordinal- or interval-type series: Kruskal-Wallis variance analysis (Siegel 1956)
  – Matched ordinal- or interval-type series: Friedman's variance analysis (Siegel 1956)

7 Minimizing the Number of Measurements

7.1 Sequential Analysis

When observing the sequential *chance* occurrence of two types of events in order to know if one type is more probable than the other, intuitively one feels the most probable is the one that happens more often. Indeed, when the difference in occurrences increases, at one point it becomes statistically significant at the 5 % probability level (or any level chosen in advance). On a graph showing the sequence of events, each one marked by an oblique dash in a specific direction (e.g., upward for one series, downward for the other), a broken line is obtained, the global direction of which leans toward the direction of the most probable event. The limits the line would cross when the difference is significant can then be drawn on each side of the central line. As soon as this happens, the experiment can be stopped (Fig. 2) (Whitehead 1997).

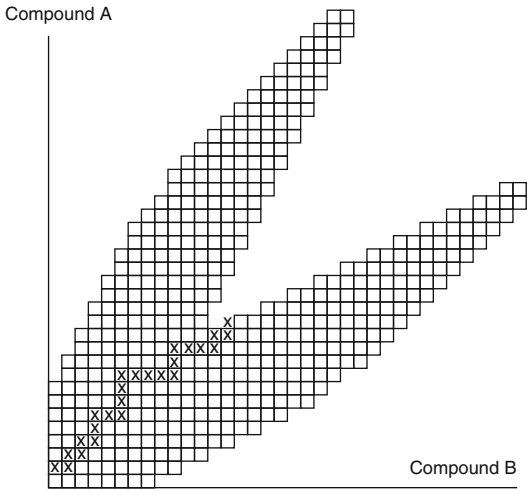

Fig. 2 Sequential trial. In the first patient, compound A was more effective than compound B, thus the first *vertical box* above the *black* one was checked. In the second patient, compound B was more effective than compound A, thus the next *horizontal box* was checked. In this example, the exit lies between the two wings of the grid, indicating no significant difference in effectiveness between the two compounds. Significance would be indicated by an exit at the exterior side of the wings

These limits can be computed using mathematic formulas which can be found in the book of Armitage et al. signalled at the end of this chapter.

7.2 Taguchi Designs

Taguchi designs are the most widely used experimental plans aimed at reaching the desired result with a minimum of experiments Taguchi and Wu (1980). For example, for the study of the effect of three parameters, each having two possibilities, it is possible to carry out four experiments instead of eight corresponding to the possible combinations. Among the categories of plans, the main types are:

- Designs with two parameters, each having two modes (L4 designs)
- Designs with three to five parameters, each having two modes (L8 designs)
- Designs for parameters with three modes (L9 designs)
- Designs allowing the combination of one parameter with two modes with parameters with three modes (L18 designs)
- Crossed designs, i.e., combining controlled parameters (as in the above designs) with so-called external parameters that are not under control.

8 Good Measuring Practice

Any measurement, especially in biology, has a degree of uncertainty, due to the nature of the measured phenomenon, as well as the measuring device and the operator. The reliability of a measurement can only be obtained if these last two factors are under control.

Equipment on the market must comply with technical standards. However, with time, performance may weaken, due to climatic, magnetic or other factors; we recommend placing the equipment on a test bench at regular intervals (for instance every year) in order to check the accuracy of its technical performance. For example, when a

device uses several pressures, are the displayed pressures correct? Does a cast meant to last several years lose its shape with time? It may be wise to check the device completely every year by measuring the equivalent skin standard. For example, the reliability of an ultrasound imaging device is checked by measuring the thickness of the layers of a stratified material. These methods are rarely used but should become common practice. Indeed, it is difficult to find standard materials that are reliable over prolonged periods. Manufacturers should assist users on this matter.

Most errors are caused by the operator and not the equipment. They tend to occur if the operator does not systematically ask: Have I read thoroughly and understood the instruction manual? Have I followed the recommendations? It is not possible to be a good operator instantly; patience, a critical mind, and experience are necessary.

The second question is related to the conditions in which the measurement is taken. Environmental conditions: temperature and relative humidity of the room must always be noted. Other conditions are specific to the type of measurement (e.g., for thermography). Physiological conditions related to the subject should be respected: minimum of 15 min acclimation to the room temperature, rest, relaxation (made easier when the test is noninvasive), thermal comfort, absence of sweating. A third question arises when subjects are their own controls: is the test site appropriate? Symmetry is no guarantee (Treffel et al. 1994), neither is proximity (Panisset et al. 1992). The random permutation of control and active sites obviates this problem. Finally a mandatory procedure is to always write down the date and hour, the environmental conditions, and an identification mark of the tested subjects, including the control subjects. Good practice in metrology implies that a manual or computerized logbook be kept with each device.

A rational catalog of possible errors sources is (Serup 1994):

1. Study design (strategic error)
2. The measuring device (technical error)
3. The use of the device (performance error)
4. Measuring conditions (inadequate laboratory facilities)
5. Selection and preconditioning of test subject (subject-related error)
6. Data acquisition, storing, and handling (data error)
7. Reporting and publication policies (explanatory mistake)

Even when these rules are observed, it is useful to know the results obtained by others. It often happens that the values given by a device in a laboratory group are not exactly the same as those given by similar equipment in another group. When new equipment is implemented, the operating team should check the reliability of their measurements on the same subjects, and know the variation coefficient (standard deviation/mean) of the measured parameters in a sample of at least 30 people. This is also essential in order to forecast the number of subjects (belonging to the tested sample) that will have to be recruited in comparative studies using this method.

For two independent samples, this number is given by the formula:

$$N \geq 2\left[\left(\in_{\alpha} + \in_{\beta}\right)s/\Delta\right]^2$$

where $\in_{\alpha}$ is the accepted limit probability for considering as true a difference Δ that does not exist (risk α): usually one takes $\in_{\alpha} = 1.96$ for a $\leq$5 % risk of error. And $\in_{\beta}$ is the risk of ignoring a real difference Δ (risk β): usually the chosen figure is: $\in_{\beta} = 1.28$ for a $\leq$10 % risk of error.

If the samples are matched (i.e., if subjects are their own controls) the formula is:

$$N \geq \left[\left(\in_{\alpha} + \in_{\beta}\right)s/\Delta\right]^2$$

Misinterpretation is forgivable. Mistakes are often made because of ignorance of what is actually measured. Upon obtaining results, the operator must ask the following two questions:

1. Beyond the object that is officially measured, what is the real phenomenon, e.g., the so-called sebum excretion rate? Possible answers are:
   - The follicular reservoir excretion rate
   - The sebaceous gland secretion rate

- The absorbing paper absorption rate
- The stratum disjunctum absorption rate

or what is the measuring method rationale, e.g., skin thickness measurement by ultrasound. The possible answer is the time for the ultrasound to go forward and backward divided by its *assumed constant* speed.

2. What is the measurement unit and why? For example, the cutaneous blood flow is measured in volts by the Doppler because an absolute calibration of the device has not been possible. A bias in the measurement technique may also alter the interpretation. It can be caused by subject and/or operator subjectivity or biased sample selection. The former problem is circumvented by using a single- or double-blind protocol, the latter by randomization of the sample or the sites so as to cancel unknown physiological variation (always use an algorithm-generated list of random numbers).

9 Conclusion

The following procedure should be followed by the operator:

1. Ascertain the reliability and accuracy of the equipment.
2. Meticulously follow all the manufacturer's instructions for using the equipment.
3. Set up the laboratory so that the material and physiological conditions of a precise measurement are routinely ensured.
4. Systematically record the above-mentioned elements on a specific logbook.
5. Determine the variance of the equipment's measures, preferably before the method is used routinely.

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Chronobiology of the Skin: Cutaneous Clocks and Biorhythms

3

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Contents

Keywords
Biorhythms • Chronobiology • Circadian • Clocks • Skin

1 Introduction

Cognizance of time and its influence on the recurring behavioral patterns of plants and animals dates back many centuries (reviewed by Reinberg and Smolensky 1983; Moser et al. 2006; Halberg et al. 2001). The study of the rhythmic time-based relationships found in biological systems has been coined chronobiology – the science of investigating and objectively quantifying phenomena and mechanisms of the biological time structure, including the rhythmic manifestations of life (American Association for Medical Chronobiology and Chronotherapeutics, www.aamcc.net/glossary.htm). Chronobiological rhythms have a profound influence on organisms by providing the temporal structure for biological processes. To "tell time," most living organisms use timekeeping mechanisms known as "biological clocks." These "clocks" coordinate our physiological and behavioral functions, thereby optimizing the adaptations to and interactions with our environment. In the last decades, hundreds of different clocks/cycles have been identified sparking renewed interest in chronobiology. In addition, the awareness of the implications of chronobiological effects has increased, and it is now

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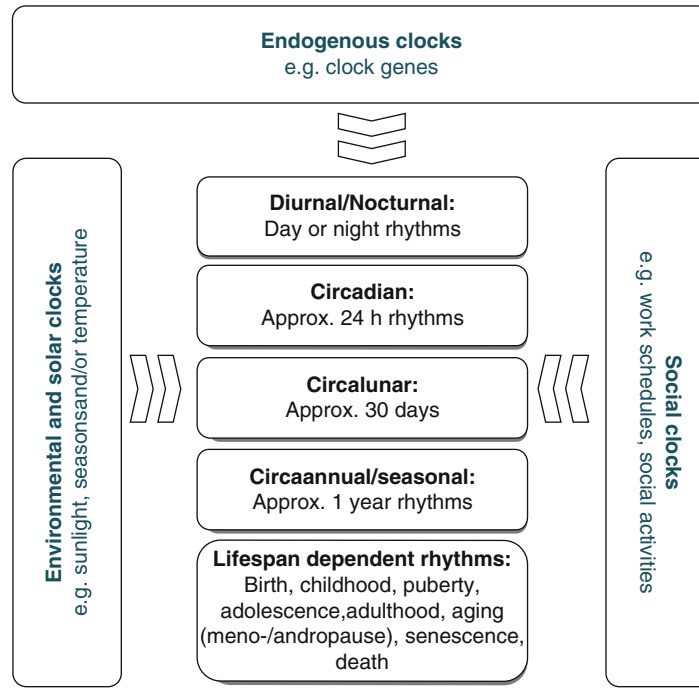

Fig. 1 Schematic representation of typical chronobiological rhythms and the clocks influencing them

recognized that these have true mechanistic and therapeutic implications (e.g., chronotherapy; reviewed by Kaur et al. 2013; Librodo et al. 2012). A short description of typical chronobiological rhythms is depicted in Fig. 1.

While the underlying science of biological oscillators is intricate and complex and therefore not entirely understood, our master clocks are most likely set according to the world's most reliable timekeeper: the sun. The circadian rhythm, the daily cycle, is probably the most pronounced and therefore the best researched. Light is assumed to be the most important zeitgeber, the external stimuli which entrain the rhythms and govern the synchronization of the circadian rhythm. Circadian timekeeping systems in mammals are organized into a complex hierarchical network of oscillators with the suprachiasmatic nucleus (SCN) of the hypothalamus acting as the principal pacemaker. The SCN receives light signals from specialized cells in the retina, the retinal ganglion cells, which entrain the SCN to light-dark cycles via glutaminergic innervation and/or photoreceptive systems based on melanopsin. This in turn triggers circadian rhythms, e.g., via the release of the hormone melatonin or adrenocorticotropic hormone (ACTH; Berson et al. 2002; Hastings et al. 2003; Luboshitzky 2000), which influences the peripheral clocks ubiquitously found in human cells. Although the exact functions are not yet well elucidated, it is reasonable to assume that the peripheral clocks are then responsible for the physiological fine-tuning leading to optimized responses to environmental and internal occurrences and processes. Biological periodicities can also be governed by other environmental cues, e.g., by the lunar cycle, but also by daily social rhythms, e.g., work. Interestingly, if left undisturbed, the "free-running" circadian rhythm in humans is approximately 25 h (possibly reflecting lunar influences as secondary synchronizers as this time period corresponds to the orbit time of the moon and with it, the tidal peaks that occur every 12 h and 25 min). One aspect that should not be forgotten is that life itself is a biological rhythm. Malfunctions of the biological clocks can lead to various disorders, including hypertension, sleep, psychosomatic disorders, and a number of chronobiological rhythms most likely out of phase in the elderly population