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Research

The long Tramp from Cellular Pathology to Molecular Pathology

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Abstract

Background: The Charité is a well-known and one of the biggest University Hospitals in Germany. Its Institute of Pathology was founded in 1831, and took part in all changes and modifications of diagnostic surgical pathology. Herein, it forms the basis to describe the history and development of molecular pathology from its early beginning. The appearance of biological structures at microscopic levels forms its fundament, similar to additional tissue theories which have been derived from cellular pathology.

Theories of pathology: Theories of pathology frequently describe reaction patterns, and try to explain the relationship between disease and its visible manifestation. They have entered pathology in the 20th century. To name some of them: theory of inflammation [Heinrich Schade 1924, [1], pathology of relations [Gustav Ricker (1924), [2], intercellular pathology [Tivadar Huzella (1937), [3].

Derivatives: The observation of principal identity of biological meaningful elements can be agglutinated to a 'general theory of live' and its manifestation. All of the investigated elements possess the same regularities, which are altered, destroyed or newly built by external influences such as disease, physical and psychological forces. Not all magnification levels that display with these elements are of the same significance. Already Virchow suggested that 'smaller elements (molecules) might be responsible for changes that are visible 'in larger elements' (at cellular level). The reflection on these ideas can be associated with the implementation of molecular techniques which has been developed in the 20th century and are still ongoing today. Perspectives: Thus, cellular and molecular pathology can be integrated under one umbrella. This umbrella will lead to newly man-formed structures, such as artificial DNA and gene components or functional chip implantations.

Keywords: Cellular pathology, molecular pathology, history, DNA, gene, chip implantation.

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Introduction and History

The analysis of history and modifications of tissue – based diagnosis is a suitable tool to understand and forecast its future development. To focus on its tramp in the Pathology Institute of a big University Hospital might serve to interpret geographical and developmental differences within a certain period. The Institute of the Charité Pathology Institute provided without any break anatomical diagnoses for more than 180 years, and, therefore, creates a founded base.

Let us propose that molecular pathology is a modification of cellular pathology which has been introduced by Virchow in 1855 [4]. Obviously, cellular pathology is based upon visible features of different kinds of tissue at certain magnifications and visualization techniques.

In the 19th century leading scientists noticed that tissues taken from creatures including man are all built by identical elements which they called cells. Theodor Schwann founded the so – called cellular theory in his famous monograph in 1839 [5].

Schwann's discovery was associated with and promoted the technical development of (transmission) light microscopes. Virchow was 18 years old at that time <Figure 1>.

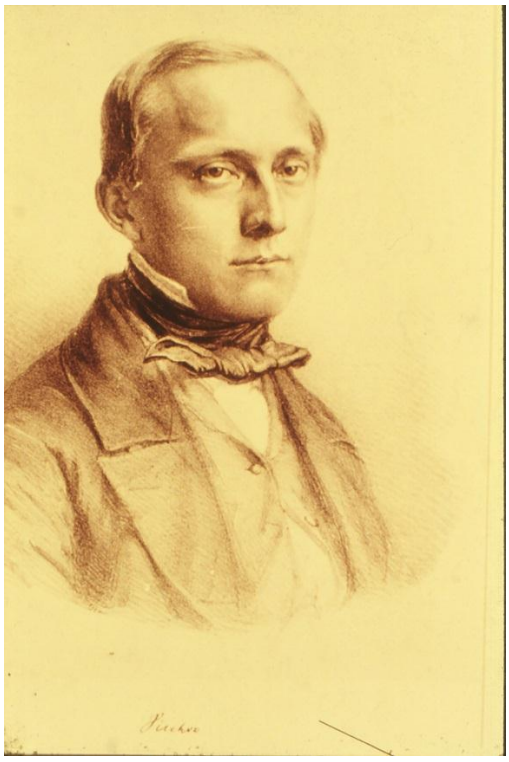

Figure 1: Rudolf Virchow (1821 – 2002) in 1848.

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He enrolled in the Medizinisch-Chirurgischen Friedrich-Wilhelm-Institut (Friedrich-Wilhelm-Institute of Medicine and Surgery in Berlin) which was founded to educate and train military doctors in Prussia in 1795, and was called Pépinière.

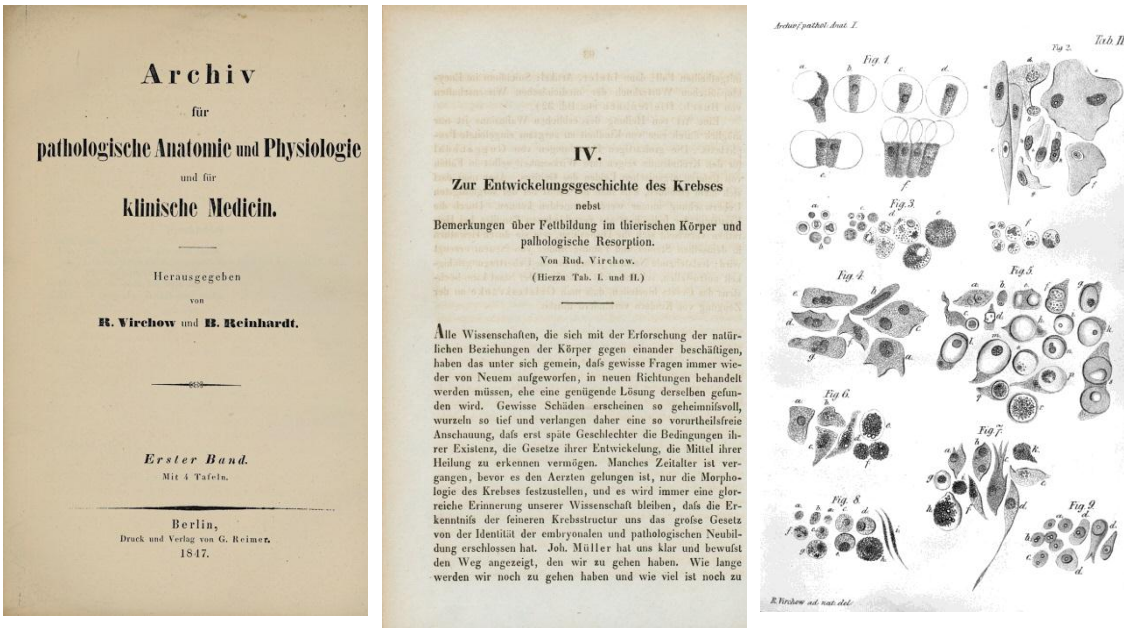
The unique cellular theory developed and spread into the medical world at the beginning of the 19th century. It fully developed around 1850.

For example: The term 'histology' was introduced by Johannis Müller in 1819 [6].

Carl Mayer (1787-1865) and Johannis Müller (1801-1858) contributed significant ideas to analyze morphology and function of cells as they were working as pathologist and physiologist at the same time [6, 7]. Their colleagues include Jakob Henle (1809 – 1885) who focused on kidneys, his student Albert von Koelliker (1817-1905) who described cellular mitoses (1844).

Virchow's contribution

Virchow started his systematic microscopic studies of cellular tissue structures in 1846. He was prosector (responsible pathologist for autopsies) at the Charité in Berlin. He published detailed drawings of normal and cancer cells in his report 'Zur Entwicklungsgeschichte des Krebses …' (History of cancer development…') in the first section of the 'Archiv für Pathologische Anatomie und Physiologie und für klinische Medizin' (Archive of Pathological Anatomy and Physiology for Internal Medicine, founded by Virchow and his friend Benno Reinhardt), already in 1847 <Figure 2a, 2b, 2c> [8-10].


Archiv
für
pathologische Anatomie und Physiologie
und für
klinische Medicin.
Herausgegeben
von
R. Virchow und B. Reinhardt.
Erster Band.
Mit 4 Tafeln.
Berlin,
Druck und Verlag von G. Reimer.
1847.
IV.
Zur Entwickelungsgeschichte des Krebses
nebst
Bemerkungen über Fettbildung im thierischen Körper und pathologische Resorption.
Von Rud. Virchow.
(Hierzu Tab. I. und II.)
Alle Wissenschaften, die sich mit der Erforschung der natürlichen Beziehungen der Körper gegen einander beschäftigen, haben das unter sich gemein, dafs gewisse Fragen immer wieder von Neuem aufgeworfen, in neuen Richtungen behandelt werden müssen, ehe eine genügende Lösung derselben gefunden wird. Gewisse Schäden erscheinen so geheimnifsvoll, wurzeln so tief und verlangen daher eine so vorurtheilsfreie Anschauung, dafs erst späte Geschlechter die Bedingungen ihrer Existenz, die Gesetze ihrer Entwickelung, die Mittel ihrer Heilung zu erkennen vermögen. Manches Zeitalter ist vergangen, bevor es den Aerzten gelungen ist, nur die Morphologie des Krebses festzustellen, und es wird immer eine glorreiche Erinnerung unserer Wissenschaft bleiben, dafs die Erkenntnifs der feineren Krebsstructur uns das grofse Gesetz von der Identität der embryonalen und pathologischen Neubildung erschlossen hat. Joh. Müller hat uns klar und bewufst den Weg angezeigt, den wir zu gehen haben. Wie lange werden wir noch zu gehen haben und wie viel ist noch zu

Figures 2a, 2b, 2c: ‚Archiv für pathologische Anatomie und Physiologie und für klinische Medizin', Band 1, (Archive for surgical pathology and physiology, and for internal medicine, issue 1), founded by Rudolf Virchow and his friend Benno Reinhardt, 1847. Herein, Virchow published an article that describes and displays cancer with drawings of cancer cells.

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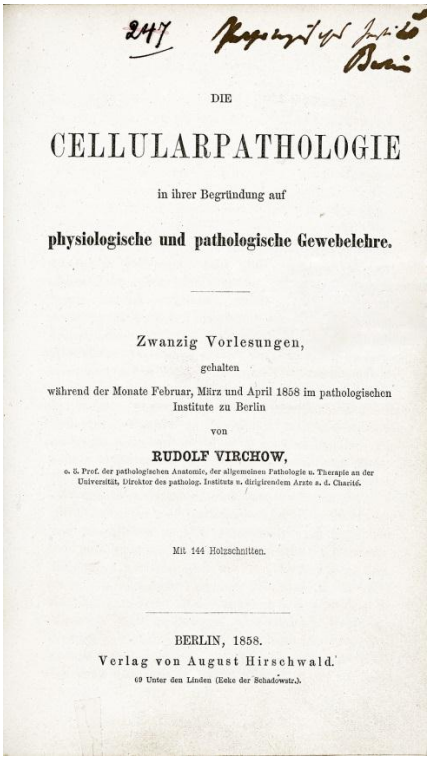
He responded to a call of the University of Würzburg in 1849, and published 'his' cellular pathology in 1855 [4, 8-10]. His research and that of his colleagues (for example Gottlieb Gluge, Julius Vogel, Friedrich Günsbach, Carl Bruch and Robert Remak) focused on cancer, also called morbid lumps [11, 12].

He observed that cells divide and multiply, and published his famous textbook on cellular pathology in 1858 <Figure 3> [8].



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DIE

CELLULARPATHOLOGIE

in ihrer Begründung auf

physiologische und pathologische Gewebelehre.

Zwanzig Vorlesungen,

gehalten

während der Monate Februar, März und April 1858 im pathologischen Institute zu Berlin

von

RUDOLF VIRCHOW,

o. ö. Prof. der pathologischen Anatomie, der allgemeinen Pathologie u. Therapie an der Universität, Direktor des patholog. Instituts u. dirigirendem Arzte a. d. Charité.

Mit 144 Holzschnitten.

BERLIN, 1858.
Verlag von August Hirschwald.
69 Unter den Linden (Ecke der Schadowstr.).

Figure 3: Virchows textbook 'Die Zellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre' (Cellular pathology and its foundation on doctrines of physiology and histology), 1858. For the first time, diseases are explained by disturbances of cells and their interactions.

Robert Remak had published this effect already three years ago 1852 [11]. Franz Julius Ferdinand Meyen (1804-1840) was a physician and professor for botanic in Berlin. He described cell division in plants as early as in 1830 [13].

However, Virchow was the first who transferred the individual observations of cell division to a basic theory of diseases. Diseases originate from changes of cell morphology, function, and cell regeneration (omnis cellula a cellula). The smallest living entity of an organism is the cell. This was a great step forward to explain the 'causes' of diseases if compared to Morgagnis dominating theory „De sedibus et causis morborum"(1761) [4, 10].

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It took a long time until his theory was modified and recruited by our present understanding and knowledge.

However, already in 1854, Virchow seemed not to be fully satisfied and asked the following questions [9]:

„Jede anatomische Veränderung ist materiell, aber ist deshalb jede materielle auch anatomisch? Kann sie nicht molecular sein? Kann nicht mit Erhaltung der Form und des äußeren Ansehens eine durchgreifende moleculäre Änderung in der inneren Zusammensetzung des Stoffs eingetragen sein? Die feineren molecularen Veränderungen der Materie sind kein Gegenstand der Anatomie, sondern der Physiologie, sie sind rein funktionell …".

'Each anatomic variation is material; however, has each material change to be anatomical? Couldn't it be molecular? Couldn't preservation of structure and appearance be associated with the general molecular composition of the substances? The subtle molecular changes of material are not a topic of anatomy, but of physiology. They are solely functional…'

Robert Rössle edited Virchows lectures and wrote, that Virchow declared in his last lecture (1855/56) before leaving from Würzburg to Berlin, that ‚molecular forces and impact must exist which found live' [14].

Forecasts and precognition of molecular pathology

Forecasts and precognition of molecular pathology started to enter the medical world shortly after or even contemporary with the establishment of the cellular theory.

Abrecht von Koelliker wrote in his „Handbuch der Gewebelehre des Menschen"(textbook of tissue theory of man) (6. Auflage, Leipzig 1889) his idea of molecular pathology [15]:

„Sollte es aber je möglich werden, auch die Moleküle zu entdecken, welche die Zellmembranen, die Muskelfibrillen, die Achsenfasern der Nerven usw. bilden, und die Gesetze ihrer Aneinanderlagerung und Veränderungen bei der Entstehung, dem Wachsthume und der Thätigkeit der jetzigen sogenannten Elementartheile zu ergründen, dann würde auch für die Histologie eine neue Zeit beginnen und der Entdecker des Gesetzes der Zellengenese oder einer Molekulartheorie ebenso oder noch gefeierter werden, als der Urheber der Lehre von der Zusammensetzung aller thierischer Gewebe aus Zellen."

At that moment when molecules could be detected that contribute to cell membranes, myofibrils, nerve fibers, etc., and found the laws of growth and function of our biological elementary units histology would start in new era. The discoverer of the laws of cell regeneration

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or of molecular theory will be honored to the same extend as that of the founder of the cellular theory' [15].

Wolfgang Bargmann gave a lecture entitled ‚nature and aims of modern morphology' at a symposium in Berlin 1968 and described the situation at the end of the 19th century: 'After Albrecht von Koelliker additional pioneers of science recognized that it will be mandatory to investigate in molecules which define live' [16].

Several technological constraints had to be cleared before achieving this aim, for example: analysis of structure and functions of DNA and RNA, to implement in-situ hybridization, to develop polymerase chain reaction (PCR) and related techniques. All these techniques are mandatory to investigate and understand molecular pathology [17, 18].

History of cellular morphology

The establishment of cellular pathology induced intensive research and consecutively development of new technologies [19]. The technique of microscopy matured in terms of high magnification objectives, specific light filters, and finally monochrome light sources (laser, etc.) [20, 21].

Tools and techniques that permit visualization of sub-cellular structures such as electron microscopes, autoradiography, or histochemistry and immunohistochemistry followed. The pathologists and scientists could investigate in molecules and cellular compartments to detect and interpret changes in disease associated morphology and function [22].

Several conferences including the international symposium on 'Die heutige Stellung der Morphologie in Biologie und Medizin' (Today's Significance of Morphology in Medicine and Biology, Berlin, 1968) display the knowledge and interpretation of pathology at that time <Figure 4> [23]. They also mirror the uprising influence of molecular biology in pathology and illustrate the limitations of morphology.

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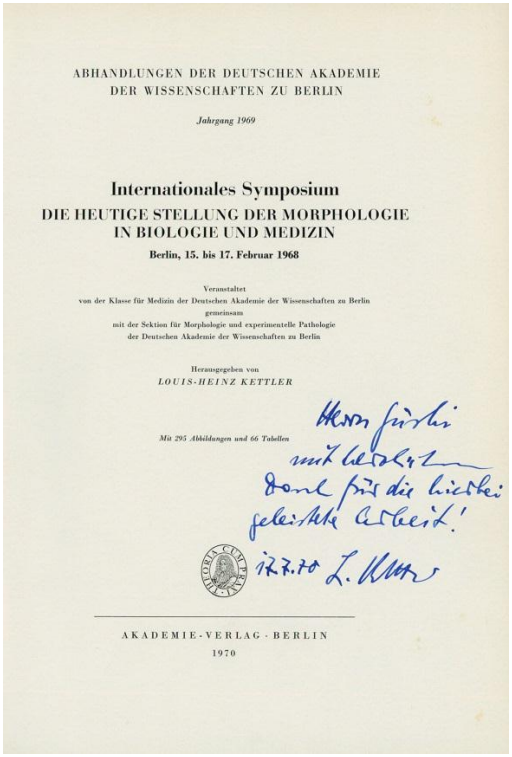

ABHANDLUNGEN DER DEUTSCHEN AKADEMIE
DER WISSENSCHAFTEN ZU BERLIN

Jahrgang 1969

Internationales Symposium
DIE HEUTIGE STELLUNG DER MORPHOLOGIE IN BIOLOGIE UND MEDIZIN
Berlin, 15. bis 17. Februar 1968

Veranstaltet
von der Klasse für Medizin der Deutschen Akademie der Wissenschaften zu Berlin
gemeinsam
mit der Sektion für Morphologie und experimentelle Pathologie
der Deutschen Akademie der Wissenschaften zu Berlin

Herausgegeben von
LOUIS-HEINZ KETTLER

Mit 295 Abbildungen und 66 Tabellen

AKADEMIE-VERLAG · BERLIN
1970

Figure 4: International symposium on 'The Significance of Morphology in Biology and Medicine', Berlin, 1968, organized by Dr. Louis-Heinz Kettler, Director, Institute of Pathology, Charité, Berlin.

On the other hand, 'fine work' on morphology did not stop. Digitalization of microscopic images, the rapid evolution and commercialization of digital cameras and computers gave rise to create mathematical algorithms to characterize and segment the visualized biological significant units [20-22]. The era of stereology, morphometry, and automated image analysis has started. It still influences pathology today and is named digital pathology [24]. Its interaction with molecular pathology, however, induced different reactions in its performance: IHC, PCR, FISH, etc. replaced tools such as electron microscopy whereas statistical and specific mathematical methods including structure analysis, feedback algorithms, data mining, deep learning systems play an important role in molecular biology and pathology [19-24].

The development of both molecular biology and digital pathology occurred contemporary and without any significant interaction at the beginning. Telepathology was one root of digital pathology, followed and finalized by implementation of standards to electronic information transfer (internet), and the contemporary maturation of image acquisition, handling of large data files [25]. Molecular pathology expanded the view to the smallest biological significant units, which are involved in intra- and intercellular information transfer [20-25].

Combined application of digital and molecular pathology was introduced in clinical application at the end of the last century [20-25]. Its understanding has induced a principal distinction of

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pathology in four categories, namely classic pathology, prognostic pathology, predictive pathology, and risk-associated pathology [20]. Classic pathology reflects to morphology at the cellular level, which has been detected and developed in the 19th century. Prognostic pathology requires in addition to the classic pathology information of extension, localization, and dynamics of the disease under investigation. Predictive pathology combines classic pathology with molecular pathology, genetics, and, partly digital pathology. Risk associated pathology is solely based upon molecular biology and genetics. Prior to its manifestation it allows to calculating the disease risk of a patient who carries certain genes [20]. The most investigated example is women who carry the BRCA1, BRCA2 gene [23, 25].

At present, education and training of medical students in molecular biology and molecular genetics has developed to common standards, as exemplarily demonstrated in the leaflet of the Charité Medical University, Berlin <Figure 5>.

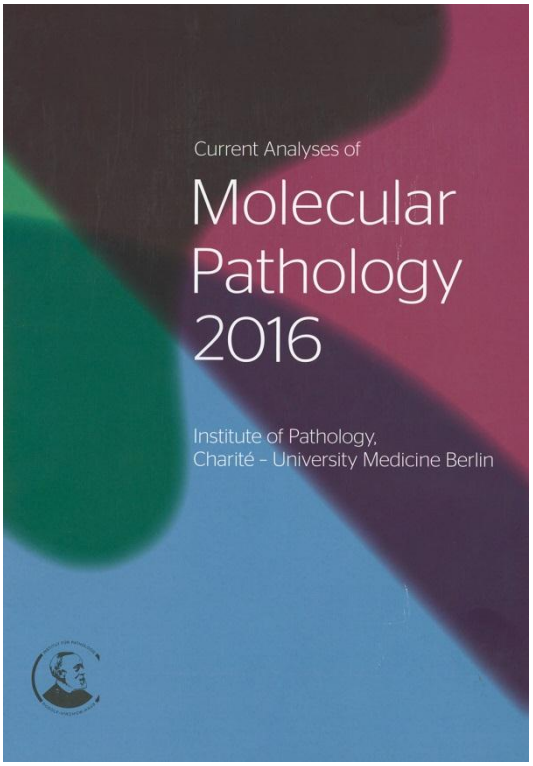

Figure 5: The leaflet of Molecular Pathology, Institute of Pathology, Charité, Berlin, 2016 describes all known analytical molecular pathological techniques.

These categories are still founded on the historic idea of pathology, namely that morphology should be clearly distinguished from its associated functions. Pathology investigates in morphology, and physiology in function [20]. Binding capacities as well as structural arrangement (folding, active spots, etc.) still express morphology. However, the wanted aim focus on function, for example on expression of genome information, binding capacities (local

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dynamic forces) etc. Therefore, we might state that the smaller the investigated tissue (or the higher the level of magnification) the more the investigation addresses function. Hold this statement true?

An explanation of this strange observation is that both structure and function are actually of the same nature. Both are an identical phenomenon that depends upon the observation period. Structures appear if the observation time is short compared to changes of the dynamic field forces that act on biological important units, functions can only be visualized when the observation period lasts sufficient long to visualize significant spatial differences of these forces. Thus, they are the same phenomenon. The difference between structure and function (or morphology and physiology) is an artefact that is caused by the fact that we can only explore our environment from our 'inside' [20].

The latest development of cellular pathology is still in its infancy. Its significance already rises at the horizon and is called liquid biopsy. Liquid biopsies combine the most important features of any disease that address therapy, namely extent and localization of the disease, and its genetic information. Radiology (HR CT, MR, etc.) explore extent and manifestation of a disease, serum analysis of genome products its hazard and potential effective therapy ((including surgery) [26].

The exploration of cells seems not to be mandatory in the world of liquid biopsies. However, it will become important again it we want to refine the model. For example, if we want to estimate the localization of a breast tumor where it will most likely become manifest in a women with BRCA1 alterations. Cellular radiology derived from cellular pathology will probably serve these patients.

Perspectives

Molecular pathology is a still growing child of cellular pathology [22-24, 27, 28]. To further allow a continuous and controlled growth some theses can be formulated:

1. Analytical and invasive techniques are needed to detect and control environmental factors that support malignancy growth. Herein microvessels and small nerves have to be mentioned.

2. Molecular actions have to be detected which are involved in social important diseases such as atherosclerosis, cardiac failures, degenerative brain diseases, or which can repair genetic disorders or replace body compartments that traumas have destroyed.

3. Infectious diseases promoted by changes of the climate, hunger, overpopulation, poor sanitation, or dangerous bacteria, parasites and transmitters should be controlled and treated by adequate molecular probes.

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Molecular biology is one important tool to invest in, and hopefully solve such problems. Its understanding and effective application requires at least basic knowledge of cellular pathology.

To our understanding the perspectives of man strictly depends upon its careful use and development.

References

1. Schade, H. *Die Molekularpathologie in ihrem Verhältnis zur Zellularpathologie und zum klinischen Krankheitsbild am Beispiel der Entzündung*. Münch. Med. Wschr. 1924. 71:1-4.
2. Ricker, G. *Pathologie als Naturwissenschaft – Relationspathologie.* Julius Springer, Berlin 1924.
3. Huzella, T. *Histologische Grundlagen einer Interzellularpathologie.* Wiener klin. Wschr. 1937. 50:1571-1575.
4. Virchow, R. *Cellular-Pathologie*. Arch. Pathol. Anat. u. Physiol. u. klin. Med. 1855. 8:3-39.
5. Schwann, Th. *Mikroskopische Untersuchungen über die Uebereinstimmung in der Struktur und dem Wachsthum der Thiere und Pflanzen*. Verlag der Sander'schen Buchhandlung (G.E. Reimer), Berlin 1839.
6. Dhom, G. *Geschichte der Histopathologie*. Springer, Berlin Heidelberg 2001
7. Mayer, C. *Ueber Histologie und eine neue Eintheilung der Gewebe des menschlichen Körpers.* Bei Adolph Marcus, Bonn 1819
8. Virchow, R. *Zur Entwickelungsgeschichte des Krebses nebst Bemerkungen über Fettbildung im thierischen Körper und pathologische Resorption*. Arch. patholog. Anat. u. Physiol. u. f. klin. Med. 1847. 1:94-201.
9. Virchow, R. *Specificer und Specifisches*. Arch. pathol. Anat. u. Physiol. u. klin. Med. 1854. 6:3-33.
10. Virchow, R. *Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre.* August Hirschwald, Berlin 1858.
11. Remak, R. *Üeber extracellulare Entstehung thierischer Zellen und über Vermehrung derselben durch Theilung.* Müllers Arch. Anat. Physiol. Jahrgang 1852, 47-57.
12. David, H. *Rudolf Virchow und die Medizin des 20. Jahrhunderts. In: Hamburger Beiträge zur Geschichte der Medizin* (Hrsg. Werner Selberg und Hans Hamm) Quintessenz-Verlag, München 1993.
13. Meyen, F.J.F. *Anatomisch-physiologische Untersuchungen über den Inhalt der Pflanzen-Zellen.* Bei Hirschwald, Berlin 1828.
14. Doerr, W. *Robert Rössle 80 Jahre alt.* Deutsches medizinisches Journal. Bd. 1956. 7:524–532.
15. Koelliker, A. *Handbuch der Gewebelehre des Menschen.* 6.Aufl. Verlag W. Engelmann, Leipzig 1889.

Hans Guski, diagnostic pathology 2017, x:246
ISSN 2364-4893
DOI: http://dx.doi.org/10.17629/www.diagnosticpathology.eu-2017-3:246

16. Bargmann, W. *Über Wesen und Ziele der modernen Morphologie.* In: Abhandlungen der Deutschen Akademie der Wissenschaften zu Berlin, Jahrgang 1969: Internationales Symposium Die heutige Stellung der Morphologie in Biologie und Medizin (Hrsg. Louis-Heinz Kettler). Akademie-Verlag, Berlin 1970, 13-18.
17. Dietel, M, et al. *Diagnostische Molekularpathologie*. Deutsches Ärzteblatt 1996, 93:A2856-2863.
18. Dietel, M, et al. *Predictive molecular pathology and its role in targeted cancer therapy: a review focussing on clinical relevance.* Cancer Gene Therapy 2013. 20: 211-221.
19. Ricker, G. *Entwurf einer Relationspathologie*. Fischer, Jena 1905.
20. Kayser, K, et al. *How to analyze Structure and Function in Tissue – based Diagnosis?* Diagnostic Pathology 2016. 2:106.
21. Kunze, KD. *Limits of Morphological Diagnostics.* Diagnostic Pathology 2016. 2:103.
22. Kayser, K, et al. *Texture and object related image analysis in microscopic images.* Diagnostic Pathology 2015. 1:14.
23. Dietel, M, et al. *A 2015 update on predictive molecular pathology and its role in targeted cancer therapy: a review focusing on clinical relevance.* Cancer Gene Therapy 2015. 22:417-430.
24. Shinkin, LN, Michailow, WP. *Über die „Neue Zelltheorie.* Sowjetwissenschaft. Naturwiss. Beitr. 1965. 176-182.
25. Sheehan, K, et al. *The Benefits of Digital Pathology in the Assessment of HER2 ISH in a National External Quality Assessment Scheme*. Diagnostic Pathology 2016. 8:170.
26. Kayser, K, et al. *Contribution of Measurement to morphologic Diagnostics.* Diagnostic Pathology 2016. 2:1.
27. Kugler, E. *Die Vorlesungen Rudolf Virchows über Allgemeine Pathologische Anatomie aus dem Wintersemester 1855/56 in Würzburg.* Hrsg. Von R. Rössle, Fischer, Jena 1930.
28. Lepeschinskaja, OB. *Die Entstehung von Zellen aus lebender Materie und die Rolle der lebenden Materie im Organismus.* Sowjetwissenschaft 1952, 32. Beiheft.