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What contribution can be made to biological monitoring by hair analysis?

Part 1

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Summary. Over the last decades there have been problems in hair analysis which have been the subject of great controversy. Great expectations were aroused for the results of hair analysis and new arguments were put forward to counter them. This meant that a method, which was applicable with certain reservations, was discredited over a long period.

This publication attempts to describe the most important factors which can affect the analysis of trace elements in human hair. Analytical methods must take in account the development and morphology of human hair and the selective bonding of trace elements on the components of the hair.

This involves a great deal of extra experimental complication which increases the costs considerably. However, economics should play a subsidiary role in the search for truth by chemical analysis.

Introduction

Biological monitoring

Biological monitoring is intended to detect the changes occuring in the human body as a result of the influence of the industrial environment. The purpose of analytical investigations is to protect the health of the worker at the place of work. Biological monitoring requires collaboration between various scientific disciplines, e.g. chemistry, technology and medicine. Basic data concerning medical and safety measures are provided by the analyis of biological materials. The concentrations lie in the µg/kg (ppb) range. This low concentration level, usually in particularly difficult media (blood, urine), makes very great demands of analytical methods. The validity of the results is checked by specific quality assurance measures [1] and standard preparations [2]. This is intended to make it possible to repeat the analytical results within the limits of the quoted standard deviations using the recommended analysis methods [3]. The accuracy of the chemical analyses allows determination of the basic biological parameters (e.g. the environmental concentrations [4] and BAT values [5]) of many substances in blood and urine.

* Based on a lecture delivered to the working circle "Analysen in biologischem Material" – Deutsche Forschungsgemeinschaft, Bonn, 8. December 1988

Interpretation of blood and urine levels

Substance concentrations determined in blood are greatly dependent on the amount of substance taken up and indicate the exposure of the whole body to the substance. The excretion of a substance as a function of time can be determined by urine analysis. The urine levels are dependent on the exposure to the substance over the previous few days and on the half-life of the substance. A good correlation between blood and urine values is an indication of a recent, uniform exposure to the substance.

The human hair stores information concerning exposure to a substance chronologically over an extended period. This could form an important source of information concerning biological functions and living conditions, a valuable contribution to biological monitoring. Is this really true?

Hair analysis

Historical

The early 1930s can be regarded as the start of industrial medical analysis. At that time Kehoe in America [6] and Teisinger in Prague [7] both demonstrated the presence of lead in the blood of persons not exposed to lead pollution – they were medical students in both cases. At that time the analysis of human hair already had a tradition extending almost half a century [8]. During the decades that followed it was the analysis of blood and urine that was subjected to further development and also received preferred treatment [9].

The possibility of hair analysis was rediscovered by nutritional scientists in the 1960s [10]. The modernization of analysis instrumentation [11], particularly the rapid development of activation analysis [12], made it possible to carry out the necessary epidemiological investigations in which the state of health was considered in the context of the results of blood, urine and hair analyses and the nutrients of the diet [13, 14]. The problems of trace analysis were always at the core of such investigations [15].

The 1970s brought us further advances in the investigation of trace elements in human hair. Two symposia in Atlanta 1973 [16] and 1978 [17] and several books [18] attempted a systematic review of recent results. The analysis was ever more frequently and in the end almost exclusively performed using atomic absorption spectrometry [19, 20].

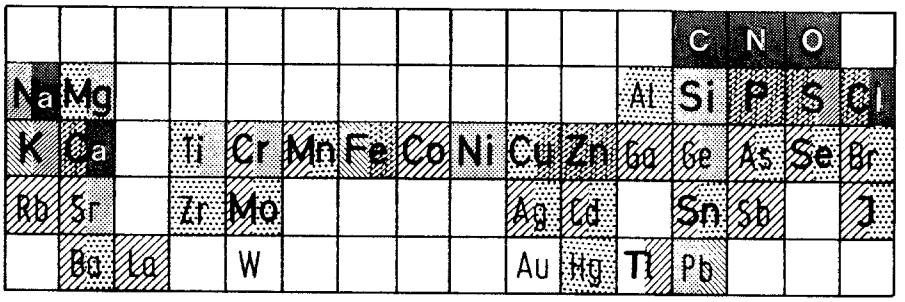


Fig. 1
Periodic system with those elements that have been detected in human hair [53] left lower conc. limit, right upper conc. limit, □ up to 0.001 µg/g, ▨ up to 1 µg/g, ▩ 1–10 µg/g, ▩ 10–50 µg/g, ▩ 50–100 µg/g, ▩ 100–500 µg/g, ▨ 500–1000 µg/g, ■ over 1000 µg/g

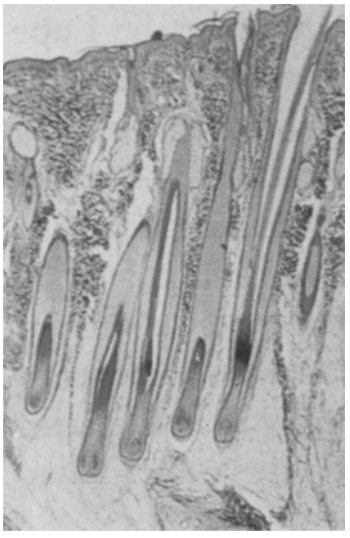


Fig. 2. Histological preparation of the scalp, with hair follicles in differing states of development (longitudinal section)

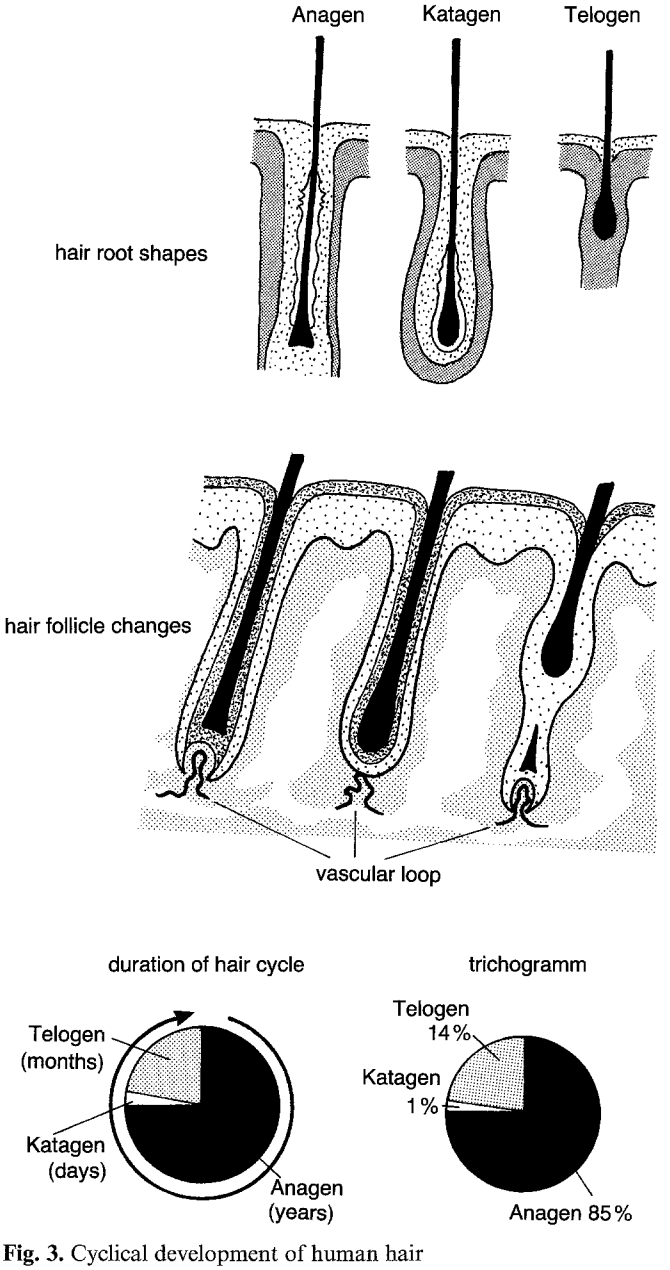


Fig. 3. Cyclical development of human hair

New perspectives were opened up in the 1980s by instrumental technology and particularly by the development of ICP spectrometry [21]. It is now possible to solve many problems successfully by multi-element determinations [22]. For well-known reasons this method of multi-element analysis was still closed for the analysis of biological samples such as blood and urine [23].

Developments in the field of hair analysis have, particularly over the past 10 years, been divided [24, 25]. Instrumental and methodological advances in biochemical analysis mean that the detection of trace elements in human hair can be carried out "almost without any difficulty". Understanding concerning the structure of the human hair has been extended [26, 27], e.g. ESR spectroscopic investigations revealed that the melanin in pigmented human hair absorbs light to protect the keratin and the scalp and, hence, the human brain from the rays of the sun [28]. The scanning electron microscope [29] and 2D-SDS-PAGE [30] have extended our knowledge of the fine structure of human hair at the molecular level.

The analysis of trace elements in hair and research into the structure of hair existed side by side but took scarcely any account of each other. The value of hair analysis came to be dramatically exaggerated [31, 32]. Some nutrition scientists, who presumably did not have any great clinical experience, made diagnoses on the basis of the concentration of minerals in hair and initiated therapy. In doing this they neglected the existence of conventional medicine with its clinical chemical arsenal [33]. This led to a distortion leading away from scientifically based medicine in the direction of esotericism. Hair analysis was "in".

Chains of "commercially orientated hair laboratories" were set up in some countries which analysed hair samples

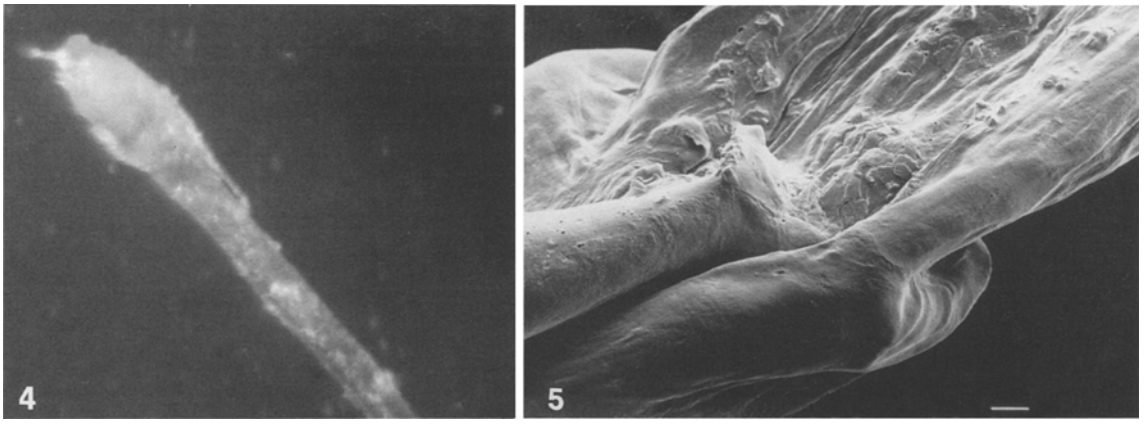


Fig. 4. Human hair in the catagen phase (micrograph)
Fig. 5. Human hair in the telogen phase (electron micrograph)

on the same bases that mineral samples or samples of cereals are assayed [34]. In modern hair laboratories the analsis data were accompanied on the computer printout by the diagnosis and recommended therapy [35]. The cost was ca. 500 DM. Privately insured patients can perhaps recover some of this, but patients who are members of the public health schemes have to work for about one week to earn this 500 DM.

The first objections to this development in hair analysis came from a reputable source, the American Medical Association. It publically posed the question: Is this science or a scam? But the American Medical Association also fell into error in its investigation of hair analysis laboratories.

The samples of hair for analysis were dispatched in just the same way as mineral or grain samples. It was pure accident that this error did not prevent the detection of the poor working methods but made them more evident.

Hair from the heads of two persons was dispatched several times to several laboratories under different names and analysed for 11 elements. The results obtained varied considerably both from laboratory to laboratory and within individual laboratories for identical hair samples. This great variability also applied to the "therapeutic recommendations" [36].

This "affair" made the scepticism and reserve with respect to hair analysis in certain expert circles even greater than it had been before. We do not wish to accuse anyone of fraud. But where did the errors come in: in the sample preparation, in the chemical analysis or perhaps somewhere else?

The development and morphology of the human hair

The individual human hair is the smallest excretion unit for trace elements. More than 40 elements have so far been detected in hair (Fig. 1).

The essential elements are printed in bold type in the Figure. The concentrations of most elements are at least a power of ten higher than they are in blood or urine. The analysis matrix of hair ought to pose fewer problems than that of blood or urine. A higher concentration and a simpler matrix should make analysis appreciably simpler. But it only appears to be so; this is the first false conclusion concerning hair analysis. The problem does not lie within the chemical analysis, it lies within the material to be analysed, the human hair.

Cyclical growth and its consequences for analysis

The histological section in Fig. 2 reveals that each hair follicle in the human skin is in a stage of development which is independent of that of the neighbouring follicles. The one is scarcely at the germ stage, while the other is in the process of dying off. It follows from this that the human hair does not grow continuously.

Every follicle possesses its own cycle independent of its neighbours. The anagen or growth phase with a high metabolic selectivity of the hair matrix (this has nothing to do with the analysis matrix!), lasts for 2 – 6 years or in a few cases even longer. There are large individual variations in this. The maximum length reached by the hair depends on the duration of the cycle (Fig. 3).

In the catagen or transition phase metabolism within the matrix ceases within 1 – 2 weeks. The dead hair root remains in the scalp, in what is known as the telogen phase, for another 1 – 6 months and then falls out.

These details of cycle duration are applicable to healthy hair. Normally 85% of the hair is in the anagen, i.e. the growth phase and 1% in the catagen. Circa 14% of the hairs have died off and will fall out over the next few months, that is they are in the telogen phase. This situation can change abruptly with the onset of disease, e.g. alopecia or intoxication with e.g. thallium, cadmium or mercury. The percentage distribution of the three hair phases in the trichogram then changes appreciably. In order to be able to determine this distribution it is necessary to pull out approximately 100 hair follicles from a particular region of the scalp. The particular hair cycle can be determined from the shape of the hair root. The bulb-shaped, thickened follicle end undergoes significant changes, which can be used to determine the phase of the growth.

The micrograph in Fig. 4 illustrates a hair follicle which must have encapsulated itself from the environment even within the scalp otherwise it would have been impossible to pull it out without damage. It has not yet died off and has contact with its environment but it is in the catagen phase.

The electron micrograph in Fig. 5 illustrates a dead, collapsed hair root.

The morphological changes to the bulbus of the hair are an expression of the biological activity of the hair follicle.

The lower, bulb-shaped follicle end surrounded by the papilla is alive (Fig. 6). It takes an active part in the biologi-

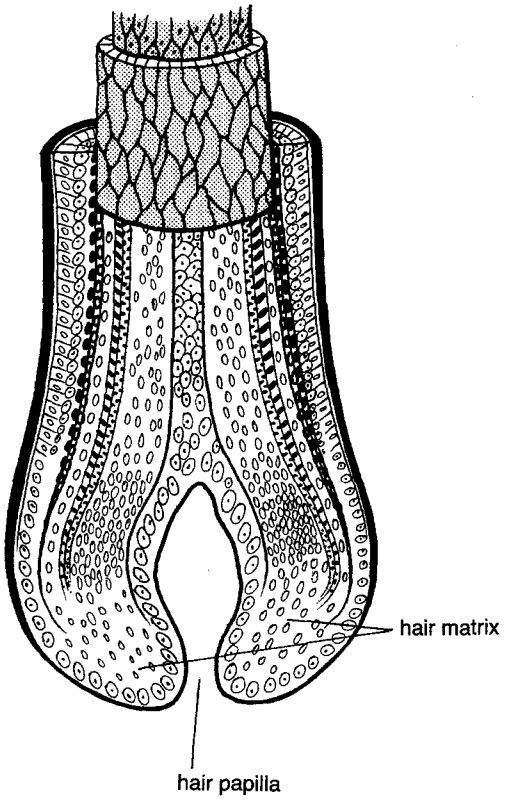


Fig. 6. Hair root

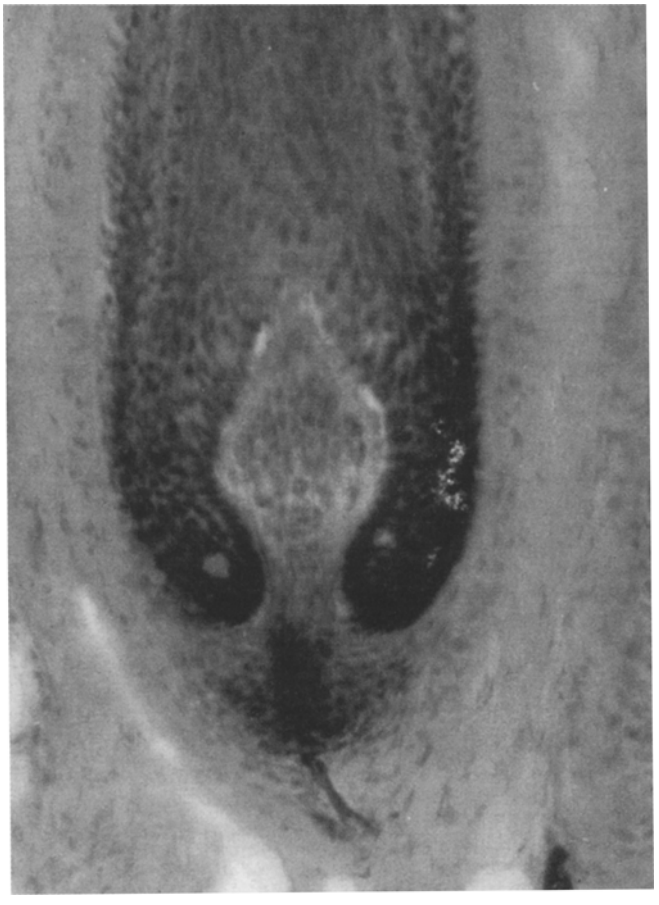


Fig. 7. Human hair root in the scalp (histological section)

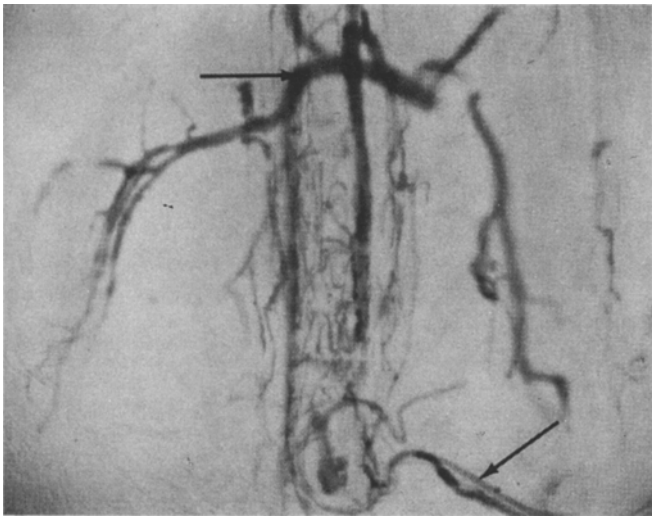


Fig. 8. Capillary blood vessels in the scalp in the region of the hair root

Fig. 9. Taking a sample for "hair diagnosis"

cal processes of the body. With regard to the deposition of trace elements this means that: The components of the hair are transported to the matrix cells through the papilla.

During the anagen growth phase the papilla is in intimate contact with the rest of the organism via the blood circulation, the lymph system and the extracellular fluid (Fig. 7). Not only the components of the hair but also the trace elements that are present are transported there in amounts corresponding to their instantaneous concentration distribution and incorporated into the body of the hair.

Each hair follicle is surrounded by a system of capillary blood vessels at the root. This ensures a continuous exchange of information between the hair root and the human organism. A narrowing of a capillary, e.g. at the position indicated by the arrow (Fig. 8), can mean "mortal danger" for the hair follicle (the same principle as that of angina pectoris).

The vascular loop of the papilla is very clearly visible here. It can be seen that the arterial blood supply is cut off. This hair follicle is in the process of dying off. The exchange of information between the hair follicle and the organism will be discontinued in the foreseeable future, but the follicle *remains* anchored in the scalp for months afterwards.

Hair sampling as in Fig. 9 yields sample material whose development phase is no longer possible to determine. It is no longer possible to characterize the hair segments

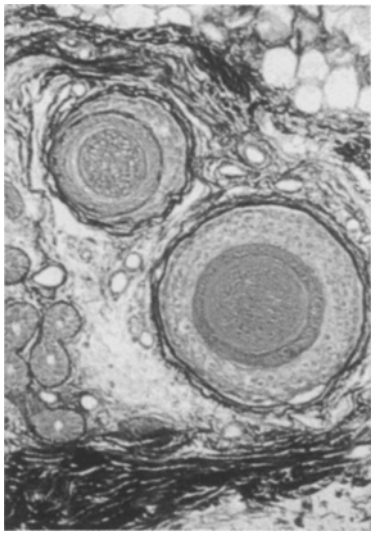


Fig. 10. Histological preparation of the scalp, hair follicle in cross section

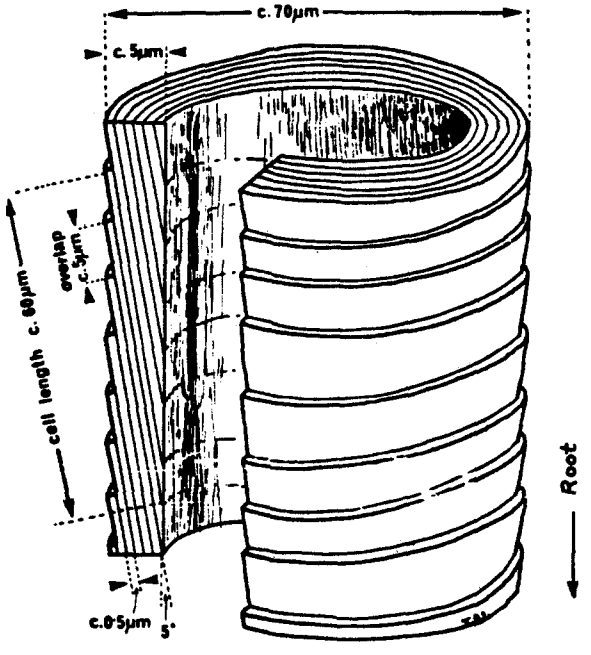


Fig. 11. The cell layers of the cuticle of the human hair according to Swift [54]

chronologically. A broad, epidemiological investigation of healthy subjects, in which hair samples were employed whose chronological classification was no longer possible, yields analysis data which are only susceptible to statistical analysis. Any deviations are compensated by the representative selection and the large numbers of samples. Such samples are unsuitable for *individual* hair analyses because: 1. The course of the element uptake, that is the exposure to elements over the last months, is unkown, 2. it is not possible to discover which parts of the hair sample are in the growth phase and which have died off.

The accuracy of the chemical analysis can be perfectly adequate, but the results of the analysis cannot be interpreted on account of the chaotic state of the sample.

The structure of the hair follicle

The fine structure of most artificial fibres is homogeneous. Fibres of animal origin, such as wool or pelt hair, have highly differentiated, heterogeneous structures.

The photomicrograph in Fig. 10 illustrates the cross section of a follicle. Three zones can be readily differentiated. The centre is the core or medulla of the hair (*a*). The next, very inhomogeneous zone is the cortex (*b*). The outer layer is the cuticle (*c*).

The cuticle is composed of four to eight flat, overlapping layers of cells (Fig. 11). Each layer of cuticular cells is separated from the neighbouring ones by a cell membrane complex. The direction of growth can be recognized even for a fragment of a hair.

The outer layer exhibits a species-specific layer of scales which is often characteristic for the individual, which is readily visible at a magnification of 400 × (Fig. 12). We have observed during our scanning electron-microscopic investigations that certain intoxications cause characteristic damage to the cuticle.

The outer layer of a healthy hair follicle can be seen in Fig. 13: There are no cracks, the cuticle has an even scale pattern recurring at regular intervals.

We have observed damage to the outer layer in antimony intoxication. The cuticle exhibits long deep cracks (Figs. 14 and 15). We have not discovered any explanation for this type of damage.

Figure 16 illustrates a hair follicle where the cell layers are primarily damaged at the edge. Frequent short, flat cracks are to be found in the scale structure of this preparation; they are even more evident at greater magnificant (Fig. 17). The cuticle has become brittle and is beginning to crumble. The sample was taken from a patient suffering from chronic lead poisoning. Figures 18 and 19, on the other hand, illustrate the hair of healthy subjets with low lead levels.

The cortex is to be regarded as the main component of human hair (Fig. 20). It is made up of spindle-shaped, cylindrically arranged cells which are 100 µm long. The ortho- and paracortical cells contain macrofibrils which are made up of ca. 1 nm long microfibrils embedded in an apparently structureless matrix [37].

Figure 21 according to Fraser [38] makes clear from right to left the ever smaller component parts from which the hair is constructed. From macrofibrils via microfibrils to pairs of helical chains and the individual α-helix protein chains of the keratin.

The hair core, also known as the medulla, is to be found in the centre of the human hair follicle. The medullary cells contain fibrous structures with numerous large vacuoles.

Chemical structure of the hair

α-Keratin

α-Keratin is the basic building block of the hair, it is a screw-shaped protein chain. Pauling and Corey [39] defined the geometric characteristics of the molecule in 1950. In 1982 Marshall [40] demonstrated that two-dimensional electrophoreses of keratin samples from different persons yield different patterns of proteins. Wittig [41] has improved the reproducibility of the person-specific differentiation

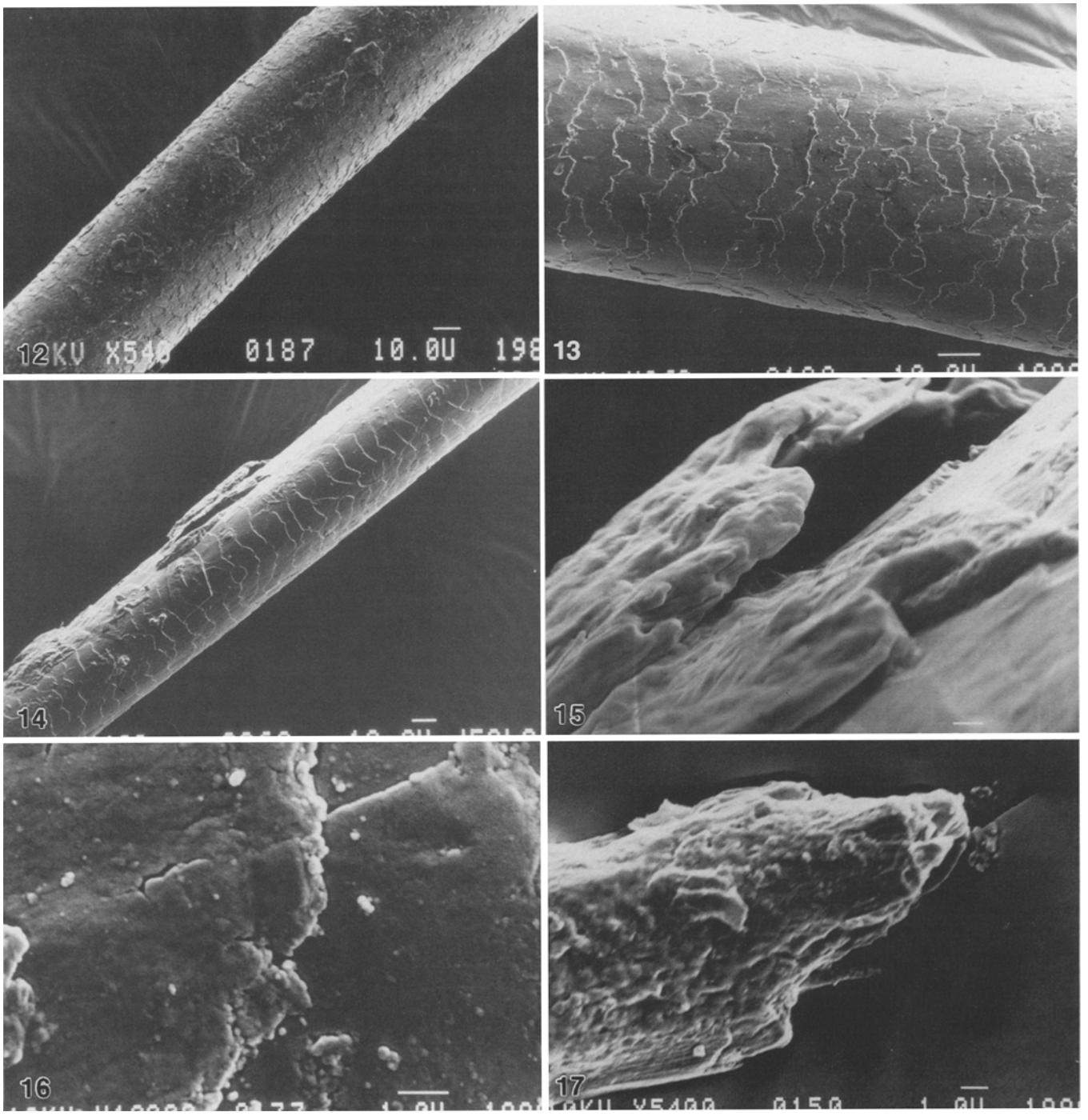
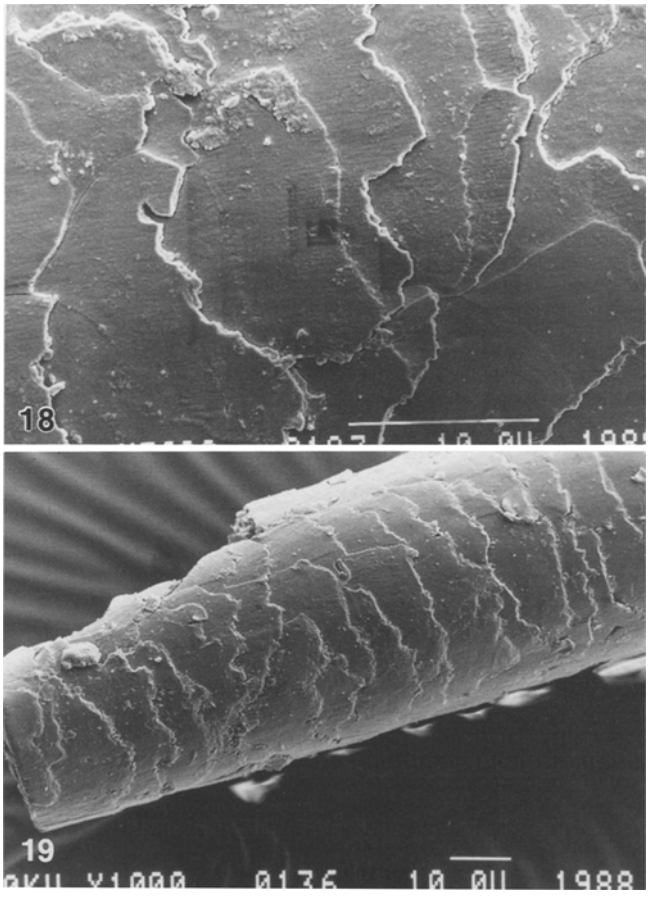


Fig. 12. Pattern of scales of human hair (scanning micrograph)
Fig. 13. Healthily developed cuticle pattern of a human hair follicle
Figs. 14, 15. Scanning electron micrographs of hair in antimony intoxication
Figs. 16, 17. Scanning electron micrographs of hair in lead intoxication

(Fig. 22). An extended familial and population genetic investigation was intended to discover whether a variant keratin pattern constituted a genetically determined polymorphism [42].

The matrix is the embedding medium for the microfibrils which make up a large proportion of the matrix. The matrix proteins contain a large proportion of tyrosine and sulphur [43]. Histological staining techniques demonstrate a high activity of heavy metals in this layer.

The matrix does not possess an α-helical structure. The X-ray diffraction pattern reveals that 30% at most of the hair substance is X-ray crystalline, the remainder is X-ray amorphous. As has been demonstrated by investigations employing nuclear magnetic resonance spectroscopy being X-ray amorphous is not the same as being without structure (β-pleated sheets and undefined conformations of peptides and proteins predominate in the immediate neighbourhood) [44].



Figs. 18, 19. Micrographs of healthy human hair for comparison with Figs. 16 and 17

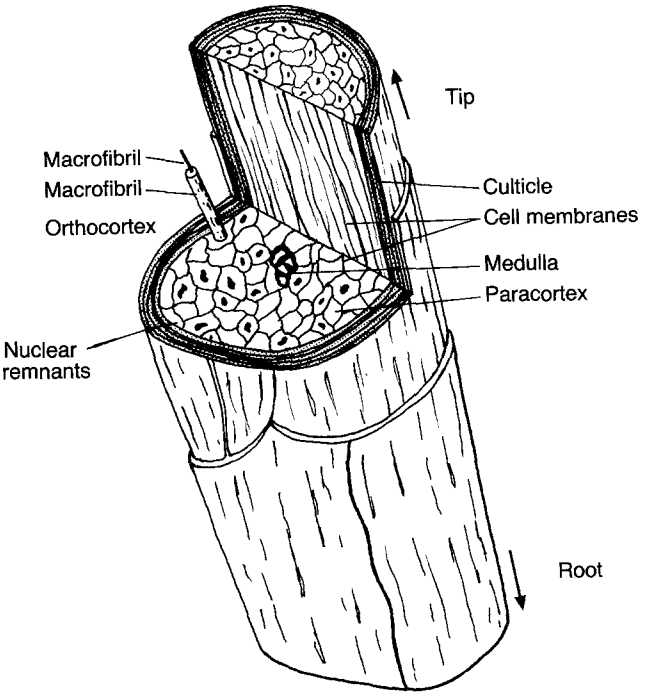


Fig. 20. Representation of human hair according to Swift [37]

Isodipeptide bridges

The medulla of the human hair contains a citrulline-rich protein with a very high glutamic acid content and very little cysteine. The proteins of the medulla differ very greatly from the keratinous proteins of the cortex. The citrulline-rich protein contains covalent crosslinks which cannot just be sulphur bridges since the cysteine and cystine-contents of the medullary protein are too low to permit this. Disulphide bridges are typical of the hair keratin. Isodipeptide bridges can be found in the cells of the medulla and the inner root sheath [45]. They are produced by catalase from protein-bound lysine with glutamine as substrate. Since no other crosslinks are to be found in medullary protein it must be concluded that the isodipeptide is very largely responsible for the insolubility of the medullary protein [46]. It also increases the chemical resistance of the medulla (Fig. 23).

Melanin

Melanin, another component of hair, is responsible for the natural coloration of all shades of hair. This intense black hair pigment is formed from tyrosine. The periphery of the cortex contains more melanin granules than does the centre. The granules from black hair are particularly hard and have a high density (1.72). Their composition is fundamentally different from the amino acid composition of the hair [47].

The intoxication processes, which have been mentioned in connection with thallium, affect the reactions with melanin. Melanin is presumably not just a hair pigment but also has other functions (see Part 2).

Trace elements in hair

The morphological structure of hair and its chemical composition make it unlikely that trace elements will be evenly distributed in it, there must be regions which incorporate them preferentially. There are indications as to the form in which trace elements might be present and experimental evidence allows the proposal of certain hypotheses.

What form do the trace elements take in the hair and where are they incorporated?

The first preliminary orientation is given by the various histochemical staining techniques with heavy metal salts. Differentiated staining is an indication of differing uptake capacities for heavy metals. The disulphide bridges are overwhelmingly found in the cortex, the isodipeptide bridges in the medulla. It seems reasonable to suppose that metal ions will be retained by different mechanisms in these two regions. Some peptide groups and, above all, the cell membrane can bind atoms and groups of atoms ionically and also act as ion exchangers.

To take an example, the lead we detect in the hair is not present in a uniform state, rather some is present as mercaptide, some in apolar combination and some ionically bonded in readily exchangeable form. The observed concentration changes on cleaning hair in various media seem to support this working hypothesis. Some trace elements appear to be very easy to release from human hair. For instance,

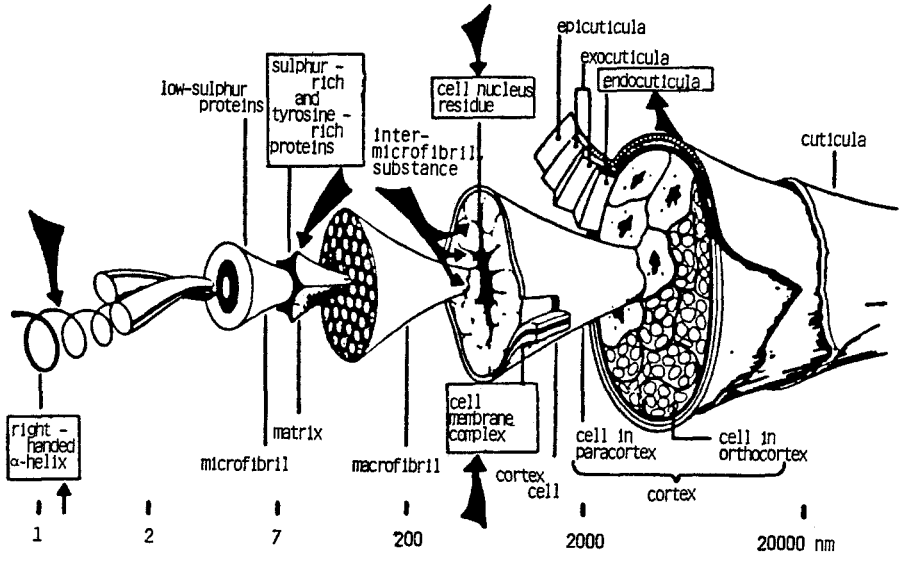


Fig. 21
Structure of merino wool according to Fraser [38]

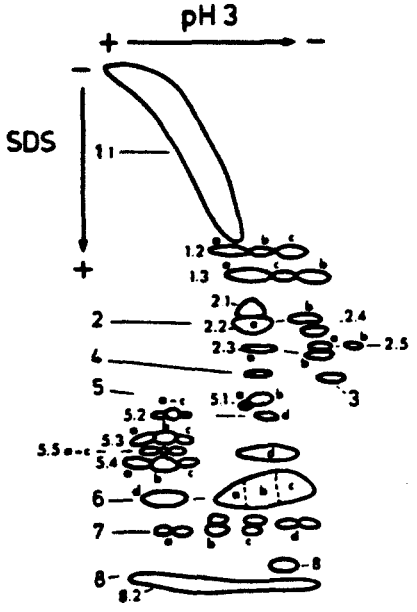


Fig. 22. Two-dimensional separation of human hair keratin by pH 3 SDS polyacrylamide gel electrophoresis according to Wittig [41]

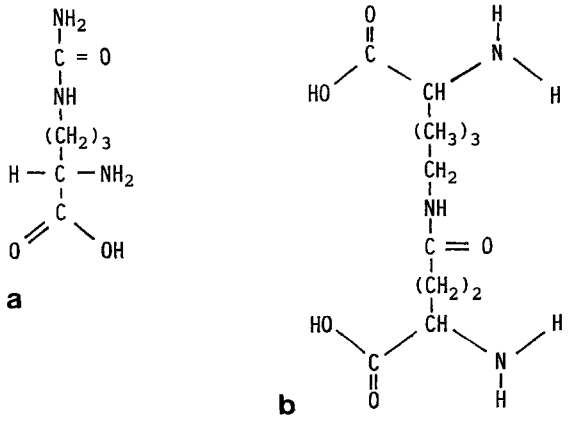


Fig. 23a,b. Important chemical structures in the medulla of the human hair: **a** citrulline; **b** isodipeptide bridge

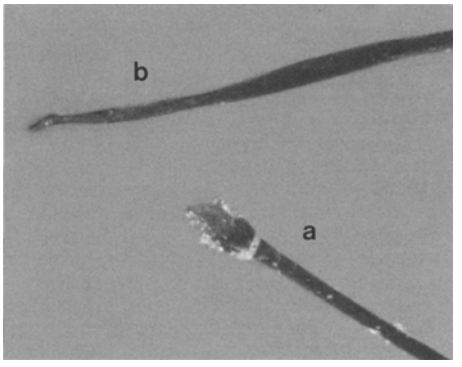


Fig. 24a,b. Morphologically altered human hair after a thallium intoxication: **a** healthy hair root, **b** pointed, conical hair root with Widy zone after Tl intoxication

some of the copper and magnesium deposits are readily washed out. However, the part of these elements which cannot be washed out must be firmly bonded to the hair.

The trace elements are incorporated into the hair in the bulb-shaped thickend part of the bulbus (Fig. 6). The amount of the element deposited depends on its instantaneous concentration in the body fluids (blood, lymph, extracellular fluid). The information concerning a single day is incorporated in a segment of hair from 300–400 μm in length.

There is a delay between the time the metal is taken up by the human body and the setting up of an equilibrium in the hair; this is ca. 35 days for lead and 40 days for thallium. This approach to an equilibrium concentration only takes place at levels below the toxic level. Higher pollutant concentrations cause the hair to die off. It is for this reason that the determination of cadmium in the hair is only applicable under normal environmental exposure. Such results cannot, on any account, be included in an industrial medical evaluation.

In the case of thallium intoxication a broad, dark, ring-shaped zone appears on the hair root on the second to third day. The root of such a hair has a pointed, cone-shaped end (Fig. 24). This effect of thallium on the hair, which was

Table 1. Human perspiration, its trace elements and their absorption onto hair [53]

Element	Concentration in human perspiration in µg/g	Adsorption onto hair after 18 h in µg/g
Na	1500	0
K	700	0
Ca	40	1.5
	0.04 – 2.86	
Mg	2.00 – 11.90	
	0.02 – 0.45	
Fe	0.24 – 2.00	40.0
Zn	0.93	
Mn	0.06	13.5
Cu	0.06	102.0

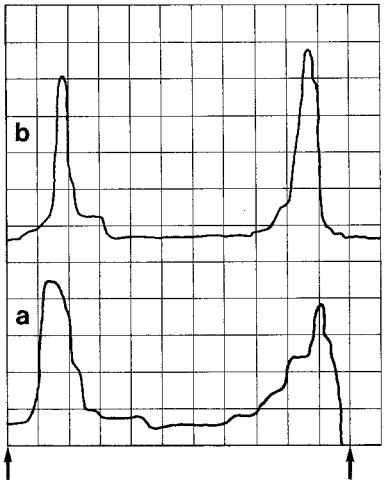


Fig. 25a, b. Distribution of Cu in washed **a** and unwashed **b** human hair after Kijewski [52], determined with the electron beam microsonde

first described by Widy [48], has been the subject of much discussion. There is a very voluminous literature concerning this subject but no information concerning the distribution of the thallium in the hair. What is the process that thallium interferes with and in what form is it found in the hair? These questions remain unanswered today for most elements.

Apart from its negative influence on the organism thallium is also able to exert a positive effect on certain biochemical reactions. According to Zaun [49] and Arnold [50] thallium catalyses the transformation of the colourless leucomelanin into melanin. The fact that the hair falls out in thallium intoxication is general knowledge [51]. It is less well-known in contrast that if a thallium intoxication is survived, it is followed by a very vital renewed growth of hair (Dosis facit venenum).

Is it possible to distinguish between exogenic and endogenic?

As the hair is formed trace elements corresponding to the body load at the time are incorporated into it.

The hair on the scalp comes into contact with the excretions of the sebaceous glands and the open-ended eccrine sweat glands. Hairs are hygroscopic. Water vapour can penetrate into their interior and is chemically and physically bound there. However, the surface of the hair is hydrophobic with respect to liquid water on account of the sebum.

It can be seen from Table 1 that human hair remains neutral towards elements that are very plentiful in perspiration. These elements are not taken up by the hair. Several authors have investigated the question as to whether external contamination can diffuse into the hair for many elements. I found a very clear experimental description by Kijewski and Lange of Göttingen dating from 1977. They used the electron beam microsonde to clarify the deposition of elements in the hair and the distribution of metallic ions in the hair's cross section.

Kijewski in his publications [52] reported the copper distribution in two hairs, longitudinal and in cross section. The arrows mark where the electron beam entered and left the shaft of the hair. The upper hair was not washed, the lower one was washed for 30 min in distilled water (Fig. 25). The lower curve exhibits a depression and broadening of the peak as compared with the upper curve. The copper ions were evidently not only dissolved out of the hair by the washing process, but transported within the hair. Washing with pure water can, thus, cause deposits adhering on the surface to be displaced into the interoir and alter the distribution of the cations in the hair. From the state of knowledge today it does not seem possible to distinguish experimentally between exogenic and endogenic burdens of trace elements in hair.

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