

K. Irrgang
U. Sonnenborn

The historical development of Mutaflor[®] therapy

with four illustrations

Translation by Gordon H. Price in cooperation with Brian Buuck



ARDEYPHARM GMBH · HERDECKE
(Germany)

Authors' address:

Dr. rer. nat. Karl Irrgang

Dr. rer. nat. Ulrich Sonnenborn

ARDEYPHARM GmbH

Herdecke, Loerfeldstraße 20

(Germany)

Preface

The administration of bacteria in the therapy of intestinal diseases dates back to researchers such as METCHNIKOFF, MORO, ROOS and NISSLE at the beginning of this century. NISSLE worked out the bacteriological fundamentals for treatment with physiological *Escherichia coli* strains, introducing the therapeutic method of substituting them by the MUTAFLOR® preparation developed by him. He was one of the first to point out the significance of intact intestinal microflora for the human organism, based on his knowledge that some *E. coli* strains have marked antagonism against intestinal pathogens.

Before the dawn of the antibiotic era, the first way of treating infectious intestinal diseases and their resulting conditions was by administering living, antagonistic *E. coli*. Later on, other functional disorders of the intestine such as chronic constipation and enteritis were also treated with MUTAFLOR®. Subsequent success in treating certain extra-intestinal diseases showed that there are mutual relationships between the intestinal milieu and other organs in the human body.

Antibiotics as well as chemotherapeutic and radiotherapeutic methods of treatment frequently lead to disturbances to intestinal microflora and regular intestinal activity. This has opened up additional fields for MUTAFLOR® treatment since the forties.

Prophylactic and therapeutic application of *E. coli* in veterinary medicine is also gone into briefly.

After the tolerance and adverse effects of MUTAFLOR® therapy have been dealt with, the last section of this publication concerns a critical discussion of the term "dysbacteriosis" (in German "Dysbakterie") – disturbed bacterial flora – coined by NISSLE.

This publication provides an historical review of the way MUTAFLOR® therapy has developed in clinical practice up to the present day. Molecular biology, which is becoming increasingly important in the scientific world, and the fact that quality requirements on clinical studies are increasing will result in new knowledge for intestinal microflora research and MUTAFLOR® therapy.

Herdecke, January 1988

Karl Irrgang
Ulrich Sonnenborn



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**A. NISSLE:
Healthy intestinal microflora is a fundamental
characteristic of a healthy organism.**

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Theodor Escherich – his life and work –

Theodor Escherich, the son of Dr. Ferdinand Escherich, district medical officer of health, and his third wife Maria, née Freifrau Stromer von Reichenbach, was born in Ansbach, Germany, on 29th November 1857. He received his school-leaving certificate from the grammar school in Wuerzburg in 1876.

After completing his six months' military service in Strasbourg, Escherich started his medical studies in Wuerzburg in 1876, which also took him to Kiel, Berlin and Strasbourg for one semester in each instance. In 1881 – again in Wuerzburg – he passed the examination enabling him to practice as a physician with top grades. After spending another six months in military service in the garrison field hospital in Munich-Oberwiesefeld, Escherich became a houseman in the Department for Internal Medicine in Juliusspital in Wuerzburg in July 1882. It was thanks to Karl Gerhardt, head of this department, that he developed his lasting fascination for the field of paediatrics. In October 1882, Escherich did his doctorate work under Gerhardt's aegis on the subject of "Marantic thrombosinusitis in cholera infantum".

Since at that time paediatrics was still just a poor cousin of most fields of medicine, Escherich decided to study for a term in Vienna in 1884, where he attended the lectures of Hermann von Widerhofer, one of the leading paediatricians of his time. He had the chair of paediatrics in Vienna – a rare position in those days – and had St. Anna Kinderspital in his charge, one of the oldest paediatric hospitals in the world. At the same time Escherich began pursuing his bacteriological studies on intestinal microflora at the Vienna Pathological Institute, which Heinrich von Bamberger was in charge of.

Escherich went to Munich in August 1884 to qualify as a university lecturer. He was allowed access to both the pathological institute under Otto von Bollinger as well as to the physiological institute, headed by Carl von Voit. Through Wilhelm Frobenius, a student of Robert Koch, Escherich became familiar with Koch's new scientific theories and working methods in the field of bacteriology. He worked with the microscope with inexhaustible eagerness for days and nights on end and demonstrated that the meconium is sterile and that bacterial colonization of the intestine occurs from the infant's surroundings within 3 to 24 hours after birth. On 14th July 1885 Escherich made a presen-

Professor Dr. med. Theodor Escherich

born in Ansbach, Germany, 29.11.1857

died in Vienna, Austria, on 15.02.1911

Discovered the Bacterium coli commune,
which was named *Escherichia coli* by the International Committee for
Bacteriological Nomenclature in his honour in 1958.

We would like to express our gratitude to St. Anna Kinderspital in Vienna,
where Th. Escherich was medical superintendent from 1902 to 1911, for providing the above photograph.

tation before the Society for Morphology and Physiology on the “Bacterium coli commune” discovered by him, which was named “Escherichia coli” in his honour in 1958. What is more, he succeeded in isolating 19 different bacteria from the intestinal contents of infants. Due to the high infant mortality rate at the time, Escherich had the opportunity to examine a wide variety of intestinal sections for their bacterial flora. He also was able to differentiate between luminal and mural microflora. His post-doctoral thesis to qualify to become a university professor, published in 1886 under the title “Infantile intestinal bacteria and their relationship to the physiology of digestion”, described his new discoveries. Proud of his clinical training in Wuerzburg and true to what he had learned under Karl Gerhardt, he made the notation on the title page: “Former houseman at the Med. Clinic in Wuerzburg.” Escherich returned to clinical work in March 1886 and was appointed assistant under Heinrich von Ranke at the Dr. von Hauner Paediatric Clinic.

In 1890, at just 33 years of age, Escherich accepted the offer of an associate professorship at St. Anna Kinderspital in Graz, where he was also appointed superintendent in the same year and professor in 1894. He married Margarete, the daughter of Leopold von Pfaundler, the renowned physicist, in Graz in 1892. Their son Leo and daughter Charlotte-Sonja were born in 1893 and 1895, respectively.

In 1902, after the death of Hermann von Widerhofer, Escherich was proposed *unico loco* and was given the Viennese chair for paediatrics and, at the same time, was appointed superintendent of the Viennese St. Anna Kinderspital.

Escherich’s numerous scientific papers – totalling some 160 publications – concern all fields of paediatrics, the physiology of infant nutrition and infant welfare. Along with his research in tetanus, tuberculosis, diphtheria and infantile scarlet fever, his papers on intestinal microflora in particular were forerunners of subsequent medical developments. Escherich not only recognized the physiological significance of *E. coli* bacteria, but also the virulence of pathogenic variants as causative agents of diarrhoea, meningitis, sepsis and cystitis. Not only the identification of the *E. coli* bacteria, but also the discovery and description of the bacterial genus *Campylobacter* made him, as a pioneer, the most successful paediatric bacteriologist.

The sudden death of Theodor Escherich in Vienna on 15th February 1911 deprived international paediatrics of its most renowned, most dedicated and most successful pioneer of that era.

Title page of the paper in which ESCHERICH described the *Bacterium coli commune* for the first time.

Alfred Nissle and his Mutaflor preparation

Alfred Nissle was born in Koepenick, now part of Berlin, Germany, on 30.12.1874 as the son of Julius Nissle, vinegar manufacturer, and his wife Mathilde, née Barsch. After taking his grammar school leaving examination, he started reading medicine in Berlin in 1893 – probably inspired by his uncle, who was practicing medicine in the Nissle home. His teachers included Emil Fischer (anorganic and organic chemistry), Wilhelm Waldeyer (anatomy), Rudolf Virchow (pathological anatomy) and Emile Du Bois-Reymond (physiology). He moved to Freiburg im Breisgau in 1896, where he took his finals in 1898 and received his doctorate in 1899 with a thesis on diseases of the sphenoidal sinus.

Nissle did his military service with the Augusta Grenadiers Regiment in Berlin from 1899 to 1900, leaving as a medical captain of the reserve corps.

Following in the footsteps of his great teacher Du Bois-Reymond, Nissle decided at first to apply himself to scientific research and become a physiologist. However, after working for 2 years at the Physiological Institute in Berlin under Theodor Wilhelm Engelmann, the fact that his efforts only served theory alone no longer fully satisfied him. Regarding this, he wrote: “The physician’s side of my attitude towards medical science grew increasingly stronger. I wanted to try to help the sick and those prone to illness directly.” He became a hygienist.

In 1903 he married Margarete, née Giesler. Their marriage, which remained childless, lasted 45 years until her death in 1948.

Nissle worked as a houseman under Max Rubner at the Institute for Hygiene in Berlin until March 1906. Then he transferred to the Institute for Hygiene in Munich (today the Pettenkofer Institute), where he worked under Max von Gruber from 1906 to 1911. He moved on to the Hygiene Institute at Koenigsberg with Martin Hahn, who had been offered a professorship there. Here Nissle qualified as a university lecturer in February 1912 in the subjects of hygiene and bacteriology. Shortly thereafter he followed Hahn, who had accepted an offer of a professorship, as first assistant at the Institute for Hygiene at the Albert Ludwig University at Freiburg. In 1915 he was appointed superintendent of the “Baden Medical Examination Centre for Infectious Diseases”,

Professor Dr. med. Alfred Nissle

born in Berlin, Germany, 30.12.1874

died in Freiburg, Germany, on 25.11.1965

Was the first to do research on *E. coli* antagonism
and introduced the therapeutic method of substituting physiological
E. coli by the MUTAFLOR® preparation developed by him.

We would like to thank Mrs. Irmgard Rochna of Freiburg,
A. Nissle’s secretary over many years, for providing the photograph.

which is still affiliated with the university's Hygiene Institute to this day. His position gave him considerable leeway. Nissle received the title of associate professor in 1917. The senate approved this appointment for "significant achievements" in the field of hygiene. He was made honorary professor in 1934.

In Freiburg Alfred Nissle was engaged in researching the antagonism of various *E. coli* strains against pathogenic intestinal bacteria. When students were growing Petri-dish cultures in bacteriological courses, he had observed that mixing human stool samples with typhus pathogens had resulted in the bacteria growing at very different rates. In some cases, the *E. coli* colonies were dominant, in others the typhus colonies. This caused him to investigate as to how various *E. coli* strains behaved when competing with pathogenic intestinal bacteria. On 20th June 1916, Nissle gave a lecture before the Freiburg Medical Association entitled "On the fundamentals for new causal control of pathological intestinal microflora". This paper was the start of a large number of publications by Nissle as to how *E. coli* bacteria can be applied in therapeutics.

After self-experiments had convinced him of the complete harmlessness of his method, Nissle first administered to diarrhoea patients "antagonistically strong *E. coli* strains" obtained from two field hospital patients, who as soldiers on the front during the First World War had not been affected by intestinal infections, even though all people in their vicinity had succumbed. In 1917 Alfred Nissle managed to isolate a particularly high-grade *E. coli* strain from the faeces of a non-commissioned pioneer officer, who, unlike his comrades, had not suffered whatsoever from any of the intestinal disorders then rampant in the region of Dobruja in south-eastern Europe. He filled the bacteria grown on agar plates in gelatine capsules sealed with wax or paraffin. At the end of 1916, the patent for the Mutaflor trademark was applied for at the Imperial Patents Office in Berlin. This name, derived from the Latin word "mutare" (= to change), was meant to express the capability of this *E. coli* strain to influence intestinal microflora. The Mutaflor preparation still uses this strain isolated in 1917 – designated DSM 6601 in the German Collection for Microorganisms – to this very day.

The pharmaceutical company G. Pohl in Schoenbaum/Danzig undertook production and sales of Mutaflor at the beginning of 1917, since they possessed special experience in the field of manufacturing gelatine capsules. In his strain collection, Nissle administered the Mutaflor strain meticulously and

Title page of NISSLE's publication, in which he described the antagonistic activity of *E. coli* and its determination

continued to concern himself with the preparation's quality. He invariably supplied the starter culture for each production batch.

As of 1938 up to his death on 25th November 1965 aged almost 91, Nissle ran his own bacteriological institute in Freiburg, which continued to be managed by his second wife Erna, née Mueller, (married in 1951), only being dissolved shortly before her death in 1970.

Alfred Nissle had transferred Mutaflor production to Hageda AG in Berlin in 1932, because Danzig as a free state had been partitioned off from the German Reich after the First World War as part of the peace treaty. The production facilities in Berlin were destroyed by bombing towards the end of the Second World War in December 1944. Mutaflor production was resumed in Hanover after the war. All rights pertinent to the product passed to Hageda AG on Nissle's death. Hageda AG relinquished their location at Hanover for business reasons in 1971, selling the Mutaflor preparation to Ardeypharm GmbH of Herdecke in February 1971.

The therapy of functional, chronically inflammatory and infectious intestinal diseases with MUTAFLOR®

Oral administration of living micro-organisms as a therapeutic measure for intestinal diseases was a topic of discussion in specialist circles as early as at the beginning of this century (66, 102). In 1907 in his book *The Prolongation of Life*, METCHNIKOFF (65) recommended taking yogurt for intestinal diseases, since he suspected that its *Lactobacillus bulgaricus* in forming plentiful lactic acid might oust pathological intestinal microflora. Positive therapeutic effects arising from administering lactobacilli were frequently observed thereafter. However, it was not possible to permanently colonize the gut by the lactic acid bacteria emanating from the food industry at that time (24, 35, 50, 54, 100).

As of 1917, NISSLE had been using non-pathogenic *Escherichia coli* – isolated from the faeces of a healthy adult – that had revealed in vitro a particularly marked antagonism against typhus bacilli for substitution therapy in the form of the MUTAFLOR® preparation (69, 70, 71, 72, 73, 75, 77, 78, 79, 80).

Since antibiotics and sulphonamides were yet to be discovered at that time, this biological live-bacteria preparation was initially used with considerable success in acute cases of infectious intestinal diseases (salmonellosis and shigellosis) as well as in cases of chronic intestinal disorders as the result of infections that had been recovered from (22, 39, 69, 70, 71, 72, 121, 125, 127). Even in the treatment of chronic typhus carriers, rapidly ensuing success was observed in some cases. However, no genuine cure was achieved, as had been expected. Contrary to patients with shigellosis that had been cured with MUTAFLOR®, typhus or paratyphus bacilli were found in the stools of most patients with recurring salmonellosis some time after administration of this preparation had been discontinued.

Subsequently, treatment was extended successfully to constipation of a chronic as well as therapy-resistant nature (73, 74, 75, 121).

In a summarizing review (74), 163 cases of non-infectious intestinal diseases were listed with marked shifts in the bacterial spectrum of the aerobic microflora and conspicuous paucity of typical *E. coli*. Included here were 63 patients with chronic constipation, 35 patients with dyspepsia and 70 patients with colitis. In 90% of all these cases, the given disturbances to the intestinal

microflora were normalized, and considerable improvement or a complete cure was achieved in most patients (73, 74, 75). It might be of interest concerning the efficacy of *E. coli* in constipation to point out that metabolic products of the bacterium have been observed to have a stimulating effect on intestinal peristalsis (1, 4).

Unanimous reports have been made in the studies conducted on substitution therapy with *E. coli* (MUTAFLO[®]) in the course of decades concerning good curative success for dyspepsia, various forms of non-specific intestinal diseases such as enteritis, colitis, enterocolitis, gastroenteritis, constipation, meteorism as well as for some cases of stomach and duodenal ulcers (7, 14, 44, 49, 50, 51, 53, 72, 73, 74, 75, 77, 78, 80, 81, 83, 88, 92, 106, 120, 121).

HUBER (41) obtained good therapeutic success in 93 infants including 66 babies with chronic enteritis, colitis or coeliac disease using MUTAFLO[®] treatment with proper diagnosis and dosage. In cases with pronounced colonization by extraneous bacteria, he recommended that treatment should first of all be carried out with antibiotics until the stool is free of pathogens, so as to then build up physiologically sound intestinal microflora by *E. coli* substitution. Earlier on, NISSLE (69, 84, 87) had recommended carrying out such a substitution prophylactically for infants, as they frequently were observed to have acquired abnormal bacterial colonization of the intestine in hospital (84). GENSCH and colleagues (23) from the University Paediatric Clinic in Cologne presented the results of a retrospective study on 1293 infants who had been admitted with infectious dyspepsia during a period of 3 years. Directly after antibiotic treatment, 425 of these children received additional *E. coli* substitution therapy in order to prevent re-infection. Unlike the group of patients treated only with antibiotic therapy, those children who had been treated additionally with MUTAFLO[®] had a statistically significant reduction in the morbidity rate regarding a second onset of dyspepsia (29.9% compared to 51.1%). Likewise recorded was an unequivocal reduction in hospital-acquired dysenteric attacks through *E. coli* substitution with Pertussis infants undergoing long-term antibiotic treatment (31.2% compared to 84.3%).

With the same basic therapy, KAISER (42a) had already arrived at statistically significant results with a smaller number of infected dyspeptic infants. Compared to a control group of 145 babies treated only with antibiotics, the number of children dismissed without recurrent dyspepsia increased from 25 to 62% in the group treated additionally with MUTAFLO[®]. The number of

infants with no relapse of infection after MUTAFLO[®] treatment rose from 36 to 61%.

MARTIN DU PAN and NOVEL (61) as well as VLCEK and KNEIFL (123) reported on similarly favourable results through substitution of non-pathogenic *E. coli* strains in treating nutritional disturbances in children.

Prophylactic implantation of physiological *E. coli* bacteria in the intestine of babies has again been adopted by Czechoslovakian and French paediatricians and clinical bacteriologists in the last few years (9, 17, 57, 58).

Nystatin treatment is initially recommended today for serious infections of the intestine with *Candida albicans* (59). Subsequent treatment with MUTAFLO[®] prevents pathogenic yeasts from re-colonizing once the anti-mycotic has been discontinued, thus ensuring therapeutic success (33, 34). Since polyene antimycotics have not been shown to affect *E. coli*, nystatin and MUTAFLO[®] may also be used for treatment simultaneously.

The efficacy of long-term treatment with MUTAFLO[®] was studied by KELLER (44) at the Medical University Clinic in Giessen on 47 adult patients, in whom a disorder of the intestinal microflora ("dysbacteriosis" according to NISSLE) had been diagnosed. The group of patients included 17 cases of non-specific intestinal disturbances (gastroenteritis, enteritis, colitis or chronic constipation), 3 of stomach and duodenal ulcers, 2 of gastric resection (BILLROTH II), 7 of tetanic conditions (intestinal spasms), 2 of cholecystopathy, 3 of chronic polyarthritis, 2 paratyphus carriers, 9 patients with carcinomata in the terminal stage as well as 1 patient each with polyposis and non-tropical sprue. After therapy was concluded, good to excellent subjective and objective curative success was recorded for all patients with non-specific intestinal disturbances in addition to stool normalization. The same was true for patients with enterogenic tetanus and the one patient with non-tropical sprue. Clinical improvement was also observed in patients with cholecystitis and cholangitis - however, the laboratory findings remained unchanged, and the microflora of the large intestine was not completely regenerated after 9 weeks' treatment. Patients with primary chronic arthritis in the advanced stage experienced subjective improvement in their condition. Of the remaining patients, the clinical picture remained unchanged for some; for others, curative success could not be solely ascribed to MUTAFLO[®] treatment with any certainty, but possibly to additional medication and/or diet prescribed as well. What proved interesting in this study was that 17-ketosteroids, the vitamin C level in the blood as well

as absorption and utilization of vitamin C were normalized during therapy in cases of successful E. coli implantation. In other words, substitution therapy directed at the intestine also had an indirect effect on other organs and functions.

Prophylactic substitution with antagonistically active E. coli may also be beneficial under certain circumstances to those with healthy intestines. Such a measure was even recommended by NISSLE for visits to countries in Southern Europe and in the tropics, where there is an increased risk of intestinal infections, as well as for epidemics, disaster areas and the like (69). A well-known example, so-called “traveller’s diarrhoea”, is primarily triggered by enterotoxigenic E. coli (19). A prophylactic dose of physiological, antagonistic E. coli (MUTAFLOR®) might very well reduce the incidence of intestinal infection (69).

Effects of MUTAFLOR® therapy on extra-intestinal diseases

Apart from the direct, immediate effects of E. coli substitution on the intestine, indirect remote effects on diseases of various other organs were observed, for which no causal relationship was initially evident. For example, curative effects on the skin, joints, nervous system, respiratory tract, cardiovascular system, bladder, kidneys as well as in cases of cancer were reported for individual patients. Regarding this, NISSLE wrote (81): “The great variety of disease processes that MUTAFLOR® has been used to cure up until now is at first a surprise to anyone. However, they are basically mere symptoms of toxin formation in the intestine resulting from ‘dysbacteriosis’. These toxins are directly responsible for intestinal disorders and thus for metabolic disfunctions, maldigestion and irritation to the immune system, as well as indirectly for unanticipated disorders in other organs and functions through remote effects. A spontaneous reaction is not to be expected from E. coli substitution. The implanted bacterium must first of all come to grips with the pathological milieu in the intestine.”

The great variety of E. coli substitution effects has been interpreted similarly by other authors (3, 4, 5, 6, 7, 11, 14, 36, 44, 45, 46, 50, 53, 105, 108, 117, 126), and likewise the possible consequences of a disturbed micro-ecology of the gastro-intestinal tract on the organism as a whole: pathological intestinal flora is believed to be the culprit in intestinal mucosa functional disorders (4, 5, 8, 14, 16, 25, 31, 44, 49, 51, 115, 116, 119). The intestinal mucosa becomes permeable for metabolic products of both pathogenic as well as non-pathogenic micro-organisms, so that polypeptides and other macromolecular substances and even living micro-organisms can penetrate this barrier at a highly elevated translocation rate (98), which then, as exogenous invaders, trigger antigenic responses. This may lead to exaggerated sensitizing of the entire organism as well as to allergic reactions to mesenchymal and parenchymatous tissues (24, 30, 48, 60, 68, 76, 94, 98, 111, 112, 118). For this reason, eczema, migraine, diseases of the joints, etc. may well be consecutive symptoms. What is more, such a change in the intestinal milieu is suspected of favouring oncogenetic processes (6, 14, 38, 52, 82, 85, 86, 92, 104a).

In this respect, DITTMAR states: “The field concerning diseases of a general nature originating from the intestine is a broad one. It is well worthwhile to

devote a great deal of effort to focal-infectious, focal-allergic and focal-toxic generalizations. My long years of clinical experience with MUTAFLOR® go to show that this preparation is not only reliably effective in local intestinal disorders, but also in the general reactions mentioned” (14).

In 5 patients with gout who were suffering from non-specific intestinal disorders and in whom “dysbacteriosis” was determined bacteriologically, therapy with MUTAFLOR® lasting several months not only led to the physiological microflora of the large intestine being restored and to the gastro-intestinal disorders disappearing, but also to uratic arthritis improving (76).

In cases of atrophic arthritis, the condition of 10 of 12 patients was improved by MUTAFLOR® treatment according to NISSLE (76). Some patients regained their full capacity to work. This trend has been confirmed in other reports (44, 79, 81, 88).

Skin diseases were also improved by E. coli substitution (4, 26, 53, 79, 81, 94, 106, 122, 124). NISSLE (79, 81, 94) published observations on the therapeutic application of MUTAFLOR® in treating eczema, milk crust, psoriasis, acne, herpes, furunculosis and pruritus. For patients having suffered from eczema for many years, several months’ therapy with MUTAFLOR® led to the symptoms largely being cured. Successful treatment of various forms of dermatosis have shown that there are interrelationships between the intestinal milieu and the skin (94). GRONAU (26) reported on milk crust occurring in babies in whom a disturbance in the intestinal microflora had been diagnosed. Subsequent to three months’ MUTAFLOR® therapy, unequivocal recession was observed in the milk crust parallel to the intestinal microflora being normalized. By administering MUTAFLOR®, URBACH (122) obtained good results in cases where itching eczema occurred with over-sensitivity to light. Studies demonstrated that the porphyrin content of these patients’ stool was clearly elevated. The pathological intestinal microflora became completely normal again by protracted oral MUTAFLOR® treatment. At the same time, porphyrin formation and thus the skin’s sensitivity to light were reduced. In the cases with skin diseases documented by LARSSON (53), all the patients were suffering from a disturbance to the intestinal microflora besides their primary disease. LARSSON reported on a patient who had been suffering from neuro-dermatitis for 32 years and whose eczema was almost completely eradicated after ten weeks on MUTAFLOR® therapy. Other authors (106, 124) mention that normalization of intestinal micro-ecology attained by microbial substitution

resulted in considerable improvement or healing in cases of chronic eczema and itching dermatosis of allergic origin.

ROERIG (103, 104) and ULRICH (121) documented several cases of partially recurring urinary tract infections caused by uropathogenic E. coli that were treated successfully with oral MUTAFLOR® therapy. JAHR (42) therefore recommended in 1926 – this means to say before the antibiotic era – that MUTAFLOR® be used in treating acute and chronic cystitis suspected of being linked to pathological intestinal microflora. In this connection it is of interest to note that RATNER and colleagues recently found statistically significant correlations between susceptibility to urogenital infections, the pathogenic bacterial species discovered and the prevalence of blood groups B and AB among the patients affected (99). It can thus be assumed that there is a relationship between blood groups, epithelial cell surface antigens and bacterial cell wall antigens necessary for urinary tract infections (99).

Remarkable results were also obtained in the field of gynaecology for individual cases of amenorrhoea, dysmenorrhoea and climacteric complaints (88, 94, 121).

Further studies discuss improvements to respiratory tract diseases (53), liver damage (7), kidney and bladder complaints (53, 94, 103, 104, 121), cardiovascular sensations (3, 53, 79, 83, 94), anaemia (79, 88) as well as stomach and duodenal ulcers (44, 49, 50, 79, 81, 92, 106, 117, 120). LEICHTWEISS (55) observed curative success with MUTAFLOR® for sciatica as well.

Interestingly enough, several authors even reported on the beneficial influence of this therapy on various psychic and neurological defects in light of a few case histories (3, 4, 79, 81, 83a, 88, 94, 106). Here it is necessary to be aware of the fact that the possibility of enteral genesis for mental illnesses was a topic of discussion in the thirties and forties (29, 63, 83a).

DITTMAR (14) recommended blood tests, as the lymphocyte count subsequent to MUTAFLOR® administration is normally observed to rise and the hyperlipidaemia to drop.

The term “extra-intestinal manifestations” is used in the meantime in gastroenterology for extra-intestinal diseases originating in the intestine.

MUTAFLOR® as adjuvant therapy for cancer patients

There is a conspicuous number of studies conducted on substitution treatment with MUTAFLOR® in cancer patients.

Very serious disturbances to the aerobic microflora assessed as being “extremely pathological” have been determined in the stool of cancer patients by some studies (6, 11, 27, 44, 45). This not only was true for patients with cancer of the stomach or intestine, but also for those whose tumor was not located in the digestive tract (86). The *E. coli* strains discovered here clearly deviated from normal strains with regard to, for example, their enzyme apparatus and their antigen character (6, 11, 27, 44, 45, 82, 114a). In this vein, KEPP and GROSSKOPF (45) found pathological intestinal microflora in 64 of 69 patients with gynaecological carcinomata. In 35 cases of genital carcinomata, BURGHARDT (11) documented without exception very serious disturbances to the intestinal microflora. HERRMANN (36) listed 50 cases of diverse cancer diseases in which the colon microflora was likewise clearly altered. He deduced from his assessment of how treatment was conducted that *E. coli* substitution is particularly helpful in gynaecological carcinomata as a supportive measure. Other studies also revealed disorders in the intestinal microflora in cases of various types of cancer that were not specified in more detail (12, 93). In addition to phenotypically changed *E. coli* or in its absence, serious *Proteus* infections were discovered surprisingly often in the stool of cancer patients (4, 6, 87, 114a). In women suffering from cancer who had been cured with *E. coli* substitution as adjuvant therapy to radiotherapy, this was invariably linked with normalization of the intestinal microflora (6, 12). However, it is not evident from the publications cited as to whether the changes observed in aerobic microflora were to be attributed to the cancer itself or to the radiotherapy undertaken as treatment.

Naturally, treatment of cancer patients with physiological *E. coli* bacteria was only assessed as adjuvant therapy in all these studies. Due to the fact that disturbances to the intestinal microflora represent a factor complicating cancer diseases, their elimination is a supporting measure, whereby in many cases improvement of the patient’s subjective condition, prolongation of life and in some cases even tumoral recession and scarring were observed (6, 11, 12, 13, 14, 28, 36, 62, 88, 89, 90, 91, 92, 93, 94, 95, 96, 106, 108, 117).

However, it should be kept in mind that MUTAFLOR® is by no means an anti-cancer drug, because it will not directly affect any tumor. Its beneficial effect on the cancer patient results from restoration of normal microecological conditions in the gut by ousting pathological intestinal microflora and thus relieving the natural detoxifying and defence mechanisms of the body (79, 86).

SAUER (107) supported prophylactic administration of *E. coli* bacteria against radiation enteritis and colitis, which causes additional discomfort for the patients being treated (18).

Using MUTAFLOR® in veterinary medicine and in raising animals

At the beginning of the fifties, ROLLE (101) reported that some pig farmers mixed the faeces of healthy animals in the fodder of sickly piglets (“runts”) in order to normalize the intestinal microflora and especially to oust enteropathogenic *E. coli*.

Similar trials were conducted later by FISCHER on piglets and by HAEFELE on cattle with nutritional disorders and diarrhoea, in which the authors administered MUTAFLOR® and reported of great success (21, 32).

BARROW and TUCKER (2) recently carried out successful studies in how to combat salmonella colonization in chickens by administering non-pathogenic *E. coli*. To prevent antibiotic-resistant intestinal bacteria being transferred from slaughter animals to man, LINTON et al. recommended feeding chickens, prior to slaughtering, with non-resistant *E. coli* strains to oust the existing antibiotic-resistant biotypes (56).

Tolerance to and adverse effects of MUTAFLOR®

Tolerance to MUTAFLOR® is good, provided that the recommended doses are kept to. Undesired adverse effects are not to be expected under these conditions.

In all the studies published about the substitution therapy with MUTAFLOR® covering a period of treatment exceeding 70 years, only very few case reports of intolerance (flatulence, diarrhoea) have been reported (92), which, however, could be traced to dosage being too high, disappearing again when the dose was reduced (41, 50, 51).

In the beginnings of MUTAFLOR® therapy, extremely high doses of MUTAFLOR® suspensions were administered on a trial basis to a few intestinally infected and seriously nutritionally disturbed babies after all other measures had failed. According to MERTZ, this led to severe dysenteriform complaints (64) so that similar tests for treating infantile dyspepsia were discontinued until well into the fifties. It was not until GENSCH and colleagues (23) as well as HUBER (41) justifiably criticized the dosage used earlier and re-introduced the therapeutic measure of subsequently treating infantile dyspepsia with MUTAFLOR® to prevent recurrence.

The following authors make special mention of the high level of tolerance and lack of adverse effects:

BRAUN documented feeding MUTAFLOR® suspensions (10^5 to 10^9 bacteria) to 9 infants with normal or hypo-acidity of gastric juices. In none of the cases was any kind of disturbance to digestion observed during or after substitution which could be attributed to the MUTAFLOR® bacteria administered (10).

GENSCH, BURMANN and GOERTLER treated 425 babies subsequent to antibiotic treatment for dyspepsia with MUTAFLOR®. There were no adverse effects observed at all resulting from MUTAFLOR® therapy (23).

When treating 93 children, 66 of whom were babies, HUBER did not note any undesirable adverse effects whatsoever (41).

KELLER (44) treated 47 adults with MUTAFLOR® and did not establish any adverse drug reactions at all.

HAUSS (34) reported on administering MUTAFLOR® to 53 patients. Adverse drug reactions or intolerance were not observed.

DITTMAR saw no adverse effects from MUTAFLOR® in over 40 years of therapy. With proper diagnosis and dosage, he considered its administration safe in all cases (14).

The term “dysbacteriosis”

NISSLE initially chose the term “dysbacteriosis” (in German “Dysbakterie”) in 1929 to combine the diseases of dyspepsia, constipation and colitis under one heading, for which he had been able to collectively observe changes in the bacterial spectrum of aerobic intestinal microflora and the majority of which could be cured partly or completely by MUTAFLOR®. He wrote: “This is why it appears expedient to me to combine the group formally denoted as ‘functional’ digestive disorders, including the tendency to same, under the etiological heading ‘intestinal dysbacteriosis’, a condition in which from case to case only one of many different main symptoms becomes manifest for a longer or shorter period of time”. The symptoms of dyspepsia, colitis and constipation were frequently observed to change, a fact which also contributed to the above observation (73, 74). At that time, NISSLE recommended not including infectious intestinal diseases in the term dysbacteriosis, although there were reports available that these diseases could be cured with MUTAFLOR® both in their acute as well as chronic stages (22, 39, 121, 127).

As early as in 1932, however, NISSLE dissociated himself from the more clinically oriented definition above and expressed himself as follows:

“What I understand under dysbacteriosis of the large intestine is any unequivocally detectable deviation of the microflora from the norm in this section of the intestine” (75).

He continued:

“Characteristics of pathological intestinal microflora are, for example, a lack of *E. coli*, *E. coli* bacteria solely in the form of dysenteric *E. coli*, and a predominance of *Aerogenes*, *Pseudomonas*, and *Proteus* bacteria. ***E. coli* bacteria invariably prove to be antagonistically inferior.** To give a collective name to all such pathological findings, I chose the term dysbacteriosis” (95).

As of the middle of the fifties, dysbacteriosis diagnostics made from stool samples faced heavy criticism as a result of newly gained know-how in medical microbiology about the complexity of intestinal microflora composition generally and *E. coli* flora in particular (20, 37, 43, 109, 110) when it became apparent that the bacteriological methods used in dysbacteriosis diagnostics to date were not comprehensive enough to be able to trace disturbances to microbial colonization of the large intestine precisely. What came under espe-

cially heavy fire was that the anaerobic microflora had not been taken into consideration and the biochemical E. coli typing used at that time was not capable of differentiating between pathogenic and non-pathogenic E. coli isolates. Nonetheless, HOFFMANN recommended keeping to the term “dysbacteriosis” in 1966 – however, in an expanded sense – in a compilation of results arrived at by the team Mikrobiologie im Schwerpunktprogramm Ernährungsforschung der Deutschen Forschungsgemeinschaft (Microbiology of the Focal Programme Nutritional Research of the German Research Association) (40): “The much-criticized expression dysbacteriosis should be retained, since it has been accepted by the [German-speaking] medical world. However, the term should be interpreted differently according to new knowledge also supported by our own studies. What we understand under dysbacteriosis is abnormal bacterial colonization of the intestine of a qualitative and quantitative nature. It not only refers to E. coli as was the most common opinion hitherto, but to all intestinal bacteria as well. Dysbacteriosis examinations thus necessitate great technical expenditure with special attention being paid to the anaerobes, their evaluation being very complex as a result. Dysbacteriosis is not a disease in its own right, but is only to be understood as a symptom.”

Further criticism against dysbacteriosis arose when it was maintained by some at the beginning of the antibiotic era and after the discovery of how to raise germ-free animals that indigenous microflora and disturbances to the intestinal micro-ecology were in no way relevant to the macro-organism. However, what is known today regarding the function and significance of intestinal microflora has shown this opinion to be erroneous (15, 47).

In their recently published textbook on human micro-ecology, KNOKE and BERNHARDT (47) offer a definition for the terms coined by HAENEL and SCHEUNERT “eubiosis” and “dysbiosis”, which according to them can be used to comprehensively describe the state of gastro-intestinal microflora. They reject the term “dysbacteriosis” from the choice of words, as it only refers to bacteria, not including fungi, protozoa and viruses, and thus is “not suitable for the complexity of a micro-ecological vantage point”. Regarding the term dysbiosis, they note: “In no event is the term dysbiosis to be considered an entity meaning disease per se and thus necessitating treatment. An absolute must here would be establishing clinical symptomatology as is defined for the microbial overgrowth syndrome of the small intestine, for example. It is not always possible to determine a definite relationship between dysbiosis and a disease. This applies in particular to the gastro-intestinal tract. However, there are

examples here indicating that dysbiosis must be considered at least a risk factor or even a symptom accompanying or aggravating a disease.”

Similar to HOFFMANN, RUCKDESCHEL (104a) defined the term “dysbacteriosis” in a recently published review on intestinal microflora. He considers the terms “dysbiosis” and “eubiosis” to be even less definable, as he does not think they should be interpreted in a purely microbiological sense (condition of the intestinal microflora), as do KNOKE and BERNHARDT, but would like to include the interactions between intestinal microflora and host organism as well. RUCKDESCHEL (104a) had the following to write about the trouble encountered with the terms “dysbacteriosis” and “dysbiosis”:

“To what extent quantitative changes within the physiological microflora are to be assessed as pathological has been the subject of protracted scientific strife. Almost from the outset there were attempts to interpret objective and putative disturbances to the intestinal microflora. Various terms were introduced to cover this, one of the oldest being dysbacteriosis, the definition of which has been subject to considerable change. ‘The common factor in all pathological changes’, taken as a basis when Nissle coined the term, is simply not evident, quite apart from the infections themselves. What is known and defined to be pathological is, however, not called dysbacteriosis. The term stands for colonization deviating from general or individual norms – in other words, it refers to a condition without providing an explanation. Dysbacteriosis is said to exist if isolated microflora constituents are either extremely plentiful, too scant or even non-existent. Such findings are based on conventional bacteriological counts and assays. [...] Finally, there is also dystopic colonization with partially well-known effects on the host organism. The best example of this is colonization of the small intestine with microflora typical of the colon and concomitant malabsorption. Diverticula, blind-loops or other anomalies provide the preconditions for this form of dysbacteriosis, which, due to its occurrence in the small intestine, can [(not) – *editor’s correction*] be determined by stool examinations.

“The terms eubiosis and dysbiosis cannot be so clearly defined. They not only refer to the status of intestinal microflora, but also include interactions with the host organism. Eubiosis defines an undisturbed relationship between the two. However, this condition can hardly be assessed by microbiological or immunological tests; at the most, it can only be gathered from how the patient feels. [...] As a disturbance to the harmonious relationship between host and microflora, dysbiosis eludes concrete definition or even measurement in all detail as well; the well-known changes are not subject to discussion here.

As a rule, isolated findings that might refer to such a dysbiotic relationship are very difficult to interpret, action and reaction in their interrelationship in particular defying clear differentiation in most cases.”

Since the micro-ecological conditions of “dysbacteriosis” or “dysbiosis” can rarely be unequivocally determined or, microbiologically, only with great laboratory expenditure, the more general designation “disturbances to the intestinal microflora” is frequently used today, above all, in English literature (15, 16, 54, 113, 114, 115, 116).

This term is also currently preferred by the Pschyrembel* editorial staff, who wrote the following: “In summary, we find that although it is legitimate to use the term ‘dysbacteriosis’, it is by no means clearly defined, leaving decisive questions unanswered (e.g. which bacteria, which harmful products?), and can therefore be replaced in most cases by designations that are more apt. The term ‘disturbances to the intestinal microflora’ is no more specific than ‘dysbacteriosis’; the former, however, has the undeniable advantage in that it does not give the reader the impression of perhaps referring to an unequivocally defined pathological process.” (C. ZINK, Pschyrembel editorial staff, pers. announcement, July 1987).

It might well be meaningful to restrict the definition of the term “dysbacteriosis” to what NISSLE originally understood by it: the lack of antagonistically active non-pathogenic *E. coli* bacteria.

As a conclusion, let it be said that the dispute over terminology should not lead to the function and significance of physiological intestinal flora being underestimated. At the ripe old age of 90, NISSLE summed up his own life’s work as follows (95):

“My objective was purely medical – to research the peculiarities of the relationship between cause and disease and, with this as a basis, to attempt to find new paths for causal therapy. General lessons and guidelines for future tasks in internal medicine can be gathered from my results. It is more rational to research the cause of an illness and to try to eliminate same by suitable methods than to predominantly concern oneself – no matter how intensely – with the affected organs, in other words with the symptoms, in the individual phases of the illness. Should we manage to combat the causes, as is the case with illnesses due to dysbacteriosis, this will then make it possible for the natural defense mechanisms to come into their own, which in turn often results in astonishing achievements.”