Irritable Bowel Syndrome – dissection of a disease

A 13-steps polemic

Reizdarmsyndrom – eine Krankheit wird zerlegt

Eine Polemik in 13 Schritten

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What we want and what we don’t

We don’t want to argue, whether irritable bowel syndrome (IBS) exists: many patients have such complaints. Nor do we want to discuss whether this discomfort significantly affects the quality of life of those affected. There is a general consensus among researchers, that patients with IBS are often neither taken seriously (enough) nor provided with the necessary help.

What we want to discuss is the way science and medicine deal with IBS. Why, even after half a century of research, there is no reasonable definition, no adequate diagnosis nor therapy. We must admit that we are not indifferent to this process, and therefore share responsibility for its mistakes and aberration. This makes it easier to pinpoint the problem; it is better to blame oneself than point a finger at others.

1. Short history of suffering of a long-lasting illness

Functional gastrointestinal disorders have existed ever since there was medicine and people with stress related symptoms such as abdominal pain. They have many names, of which we only know a few today (irritable colon, nervous bowel, etc.). Only the digital
scientific documentation (PUBMED) has made it possible to achieve a uniform conceptuality. A critical assessment of the situation until 1990 was published by Ken Klein in a groundbreaking paper [1]. Subsequently and since about 1990, a group of self-appointed experts decided to standardize the criteria for functional gastrointestinal diseases, especially to improve clinical trials with new and better medicines. These experts met time and again in Rome, making this the Rome Consensus Commission.

What have we achieved from this? After 5 editions of these consensus approaches in less than 20 years, we are now dealing with 32 different functional disorders. A journal paper each in 1989 and 1990 was followed by a whole issue of a journal (Rome I, 1992), a book of about 200 pages (Rome II, 1999), one with more than 500 pages (Rome III, 2006), and a two-volume edition (Rome IV, 2017) [2, 3]. The barbarians are not at the gates of Rome, they are already inside [4].

2. All roads lead to Rome, why does none lead out?

Taking the Rome criteria into account, one finds fairly quickly that it’s a self-sustaining system: The criteria exist, they generate pressure even where they were not originally intended, for example with the publication of scientific results. From then on, all study publications had to declare that the included patients were selected from Rome I (and over time Rome II, Rome III, and soon Rome IV), even if at that time, valid translations of the relevant questionnaires were not yet available in most countries.

3. On the use and abuse of epidemiology for life

In order to emphasize the importance of a disease (or of 32 different diseases), it is important to know its distribution in society, and not just its occurrence in medical care (practices, hospitals) – why?

Epidemiology can show necessity, but it can also increase or decrease it, depending on the question. The blur in diagnostic reliability (do you have IBS = do you have symptoms that are compatible with IBS?) becomes a method in the Rome Criteria. When answering the simple question: how often does IBS occur, requires the evaluation of 50 questions from the Rome Modular Questionnaire (RMQ), epidemiology becomes a farce. Although there is up to 30 % overlap with other functional gastrointestinal disorders [5], according to the Rome criteria one has to have either IBS or functional dyspepsia (FD): tertium non datur, period!

4. How frequent is frequent: epidemiology or counting peas?

According to nearly 100 epidemiological studies in more than 40 countries, the population prevalence of IBS varies between 3 and 30 % [6]. There is absolutely no trend visible between countries or continents. Countries with comparable health care systems can report significantly different values, whereas countries with different systems report similar. Third world countries are sometimes higher and sometimes considerably lower than US and Europe. When it comes to IBS prevalence, the comparable situation in South America becomes incomparable. This difference is usually blamed on the survey tools asking different questions, and not the 50 questions of RMQ.

However, that is not the whole story: The use of the Rome criteria in one survey sample (n = 643, Olmstead County, MN, USA) showed [7] that the prevalence varies with criteria: 25.7 % becomes 4.8 %, 6.8 % and 4.7 % for Rome-1989, Rome-1990, Rome-I-1992 and Rome-II-1999 respectively. When Rome-II was compared to Rome-III, Rome-III reduced the prevalence again [8]. The same is already happening for Rome-IV (8a): abdominal discomfort is not a valid symptom anymore, it has to be abdominal pain. This is not a fluctuation of the prevalence, the patients are not cured but simply disappear from the statistics, or they come back again with new complaints; this is uncertainty of the measurement of prevalence. While patients are still sitting in the waiting rooms for therapies, they have now lost their diagnosis.

5. Reality is less than the sum of its parts

Epidemiologically, the population is composed of groups suffering from irritable bowel syndrome (~15 %), chronic back pain (~15 %), headache (10 %), joint pain (10 %), chronic fatigue (10 %), fibromyalgia (10 %) depression symptoms (15 %), food intolerances (15 %), and other somatoform and psychosomatic disorders. There are two plausible conclusions, first: All people in western nations suffer from one or another disorder of this kind. This would then be a normal state, and by no means a disease. Second: Some people accumulate many of these discomforts. This is very likely, because the same numbers are repeatedly reported by various medical disciplines [9].

6. One or many diseases, a matter of perspective

Whether a specific set of gastrointestinal symptoms should be named IBS should be determined by experts in the field of gastroenterology. In spite of this, most patients are probably not seen by gastroenterologists, but instead by general medical practitioners. A recent international survey showed [10], that the majority of them (two out of three!), do not care what the gastroenterologists (or the consensus experts in Rome) have to say. Instead, they assess IBS as they have always done for more than 50 years. This comprises the exclusion of important organic diseases and implicitly according to the still valid criteria of their specialist society, e. g. the so-called WONCA criteria of general practitioners, which are also displayed in the valid ICD-11 code. The fact that IBS is now regarded as an organic disease [11] has not completely sunk in.

But there is another perspective, another player in this game, who, ignored by gastroenterologists, in return largely ignores gastroenterologists. It makes its own definition of functional disor-
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7. Where is biology in the bio-psycho-social model?

Paradoxically, many physicians who, thankfully, are concerned with functional syndromes and are interested in them, do not know much about the biological and cellular processes, which they learned a lot of in their medical training. While many psychologists, in whose studies biology plays a secondary role, are fascinated by biological processes.

It is more than surprising that the apologists of a “biopsychosocial model” of illnesses, who are equipped with medically sound knowledge, are more fond of using vague psychological constructs such as personality, stress, emotions, affects, attention etc. [12], instead of considering the common biological-somatic causes of the above-mentioned functional disease syndromes. The latter is much more likely than the existence of a more or less common psychological condition, at least they would be easier to empirically verify. A gastrointestinal infection can not only lead to an irritable bowel syndrome [13], but also functional dyspepsia [14], chronic fatigue syndrome [15], fibromyalgia syndrome [16], overactive bladder [17] and who knows what else [18].

8. Head and gut: one human, two brains, three options

Since the second brain of man – the abdominal brain – is being spoken about, almost every journalist and many laymen, but hardly any neuroscientist or gastroenterologist talks about the fact that there is a second decision-making authority that controls “decisions from the belly”, beyond complex networks of the “first brain”. It seems plausible to imagine “intelligent networks” (plexus) in the intestine, which can be held responsible for stupid ideas of the brain or mood swings caused by serotonin produced in the intestine, apart from the fact that this serotonin, thankfully, never reaches the brain, otherwise we would probably all be zombies with continuous mood swings with perpetual emotional ups and down.

The question “what is IBS” is raised again: presumably, it is not just one disease, but it is at least two: mental (in the case of the brain) and enteric. Probably, however, it is rather three: mental, enteric, and one of the communications between the two, which could further be subdivided according to sensory and motor pathways. In our mind, this is still better than to classify patients by symptoms (IBS-D, IBS-O, IBS-U, IBS-M), which has led us around in circles for 25 years, but never forward.

Just as diarrhea is not the same as diarrhea, constipation can have very different forms, as well as causes and also abdominal pain (not to mention abdominal discomfort). IBS is rather the expression of different disorders of the intestinal functions as their pathophysiological markers. Rome IV attempts to take this into account, that disturbances of the brain-gut axis are responsible for functional gastrointestinal disorders, but this falls short: it is only a shift of the cause into the unknown, towards “trans-nasal”.

9. Chicken or egg: when is a disease a disease?

Back to the already discussed problem of the diversity of functional / somatoform disorders (We deliberately abstain from a decision for one or the other concept): If 30 % of any population suffers from complaints, the question is whether one is affected by a disease or some epidemic effects of behavior.

This problem is very common when it comes to obesity: If 50 % of the (American) population eat so that they are at least overweight according to the nutritionists criteria, medical consequences may arise from them, which are pathogenic and are economically relevant (in many but not all), and therefore require intervention. Obesity, however, is not per se a disease but it is rather a socio-economic problem and/or an individual behavioral problem.

IBS emerges, when on one hand nutritional-, bowel-, health behavior, and on the other hand, expectations of complete medical care enter into an alliance. What was previously a mood disturbance with a spectrum ranging from temporary postprandial (“gourmet couple syndrome”) to chronic “irritated stomach or intestine” – becomes a disease of epidemic proportions. This is supported by the fact that it has been given a name, that it has a global epidemiology (see above), that the very different pathophysologies are ignored. And we are led to believe that there is a chance for the “magic bullet” therapy, if we only stick to solid scientific rationale, e. g. guidelines on the basis of Delphi method-based processes.

10. Guidelines should guide, not misguide

A two-volume opus like the Rome-IV criteria cannot, of course, be a guideline anymore, perhaps a reference book for curious academics (“What does Rome say about abdominal pain in children?”). The 70 pages of the German S3 guideline of 2011 cannot be one either (that’s why there is a handler short edition in English, but do German doctors read English guidelines?). Unfortunately, data are still lacking showing whether and to what extent gastroenterologists and general practitioners know and follow the guideline at all. With the involvement of more and more medical specialists, the correct detection rate of IBS cases increased from 30 to 90 %, while it is above 85 % at all levels of expertise for in-
flammatory bowel diseases in a case vignettes study [19]. These numbers suggest that the guidelines are either not known or ignored; in any case, they have obviously missed their primary goal to serve as a manual in daily practice.

11. Using a sledgehammer to crack a nut: diagnostics yesterday, today, and tomorrow

According to the above cited survey among general medical practitioners [10], the majority of them still follow the rule that IBS is present after relevant organic diseases have been excluded. The diagnostic effort is limited to physical examination, laboratory testing, sonography, and if necessary endoscopy. Special examination is recommended by most guidelines only in exceptional cases or for scientific purposes. After this, the therapy follows: symptom-oriented (pain, diarrhea, constipation, flatulence), pragmatic and/or by way of trial and error. Up to this point, the S3 German guideline and symptom-based Rome criteria fit together, despite their different purposes: here harmonization of practice, there harmonization of clinical trials. Both agree that a one-time diagnostic work-up and a one-time stated diagnosis is best for everyone: physician safety, patient safety, and cost control.

With the pressure to increasingly acknowledge pathophysiologic concepts and to refrain from solely symptom-based diagnosis the problems will rather increase. Based on the numerous putative biomarkers that are now discussed in IBS and FD (and some for both diseases) [20], doors are widely open for special examinations, however, for a clinically undefined subpopulation. This would cause a cost explosion, for which there are initial indications [21]. There is a need to revise our thinking: a costly diagnostic and therapeutic work-up only for a serious disease as defined by generally accepted criteria. Hence, we urgently need studies dealing with objectifying the severity of IBS.

But, there is another solution: in the mid-eighties, when the diagnosis of lactose malabsorption became a routine with the H2 breath test, some of the supposed IBS patients became patients with a specific food intolerance, which, if not treatable, were at least manageable. In cases where a disturbed bile acid metabolism was found to be the cause of complaints in some IBS patients [22], they were then treatable and thus should disappear from the IBS statistics. This is the only way biomarkers make sense.

12. The boon and bane of pharmaceutics for IBS

The Rome process, as well as the other consensus procedures led us to believe that IBS is a clearly delineated or demarcated entity (at least IBS-D and IBS-O), and therefore, easily managed by pharmacological treatment. However, drug development has so far faced over and over the same paradox: relatively small drug effects (5 to 15 %) on top of relatively large placebo effects (~ 40 %) [23]. Not only do all pharmaceutical companies prefer herd mentality (for example, all on the serotonin trail), they also do not learn, not even from the mistakes of others, let alone from their own. Why not develop an ‘orphan product’ with defined indication and decisive benefits (intestinal pseudo-obstruction, diabetic gastroparesis, constipation in neurodegenerative diseases, neurogenic diarrhea / incontinence) and wait and see whether the IBS market opens up (as did the market for PPIs in functional dyspepsia, whether sensible, let ’s leave aside)? Instead, attention is always paid to the whole, i.e. cure all IBS patients – economical perhaps comprehensible, medically and academically still nonsensical. Failure of propagated blockbusters is foreseeable, as IBS it is just not a single disease entity.

13. The uncommon common sense?

The ‘common sense’ or the ‘clinical experience’ suffers from two things. On one hand, both are always only used if a different opinion is justified, or if both differ from a well-controlled clinical study. It would be very helpful if clinical experience were to be used as an empirical report, independent of experimental evidence in randomized controlled trials and before clinical trials reveal empirical evidence. For this purpose, however, it would be necessary to integrate all practitioners with experience into ongoing observational studies (‘real world studies’). This is not only missing an appropriate methodology, but also interest of doctors, industry and care institutions, above all the health insurance plans.

On the other hand, ‘clinical experience’ cannot be a self-declared feature of individuals and institutions (as is so often the case) without further objectification. How many IBS patients have you seen, diagnosed and treated before you can claim experience with IBS? Does this not also depend on the level of the care system (primary, secondary, tertiary)? The Rome Consensus Group has published, with the issue of the Rome-IV criteria, a table [3] which specifies which type of IBS patients are to be found at different care levels and how they differ with regard to age, gender, severity of symptoms, co-morbidity, loss of quality of life, and so on. It is not clear whether this is an empirical distribution of IBS patients or whether this reflects the collective experience of the Rome experts from different countries or the experience of the author of the article. In any case, it is necessary to check whether this distribution also applies in each country with a different health care system. It could only then be a benchmark with which the experience of an individual doctor could be measured. Finally, we need to install a possibility of a ‘certification’ as a specialist for IBS or for neurogastroenterology.

The future of a turbulent past

When Thomas Frieling and Paul Enck were in training in the 80 s of the last century with Martin Wieniebeck in Duesseldorf, one with a clinical and the other with a psychological-scientific background, we occasionally thought that, unlike the ancients, we would eventually see the ending of the clinical enigma IBS. Thomas Frieling and Michael Schemann conducted the same discussions in Jackie
Wood's lab in Columbus, Ohio, that the pathogenesis of IBS, if not completely elucidated would at least largely be clear before they retire. Occasionally, the three of us mocked ourselves about the minor progress.

Now, 35 years later, we have to realize that our hopes have deceived us. Like the giants, on whose shoulders we stand, we haven't advanced further than the next mountain which is still to be climbed. Whether solution of the IBS riddle awaits behind the next cliffs is undecided and left to the decision of those who come after us.

We have collected our neurogastroenterological knowledge – together with that of many colleagues – in a textbook (Neurogastroenterologie, De Gruyter Berlin 2017). We have attempted to reach Jane and John Doe with a popular science book (Darm an troenterlogie, De Gruyter Berlin 2017). With this polemic, we have tried to write the frustration off our chest about what was not achieved, and to prepare those who are coming after us for the frustration – honi soit qui mal y pense.

Conflict of Interest

The authors declare that they have no conflict of interest.

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