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Wheat Syndromes

How Wheat, Gluten and ATI Cause Inflammation, IBS and Autoimmune Diseases

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Preface

This book is different from any other book on wheat, gluten, and nutrition because it is a profoundly medical book. Although it is a profoundly medical book, not one of the many a-little-bit-medical but otherwise popular guidebooks on lifestyle, diet, or cooking, we can assure you that it won't be dry or boring. On the contrary, we would like to take you on for a thrilling journey of discovery and insight, a scientific and clinical expedition to which we have dedicated decades of our lives as researchers and clinicians. When we took off on our exploration, well equipped with a reasonable armamentarium and curiosity, we didn't know what we were going to find, and it is still surprising for us which previously unknown realms we had entered and got to know. We would like you to join us on this journey and invite patients, doctors, and everybody interested alike.

What we have found is completely different from anything you have ever heard about in the fields of nutrition or medicine. We are all used to the observation that people tolerate different foods better or worse, but our food does normally not cause serious harm (apart from common allergies) or make people seriously ill when consumed in moderate amounts. This is what distinguishes food from the inedible. You might reply: But some authors and books claim exactly this—that foods can be poisonous, especially wheat and gluten. We would answer back: Where is their scientific and mechanistic evidence? Where are their scholarly papers? Have these authors got involved in the hardships of scientific expeditions and clinical studies? We would be open to learning about their evidence—we cannot see it. If our insights were not really new and different, we would not have written this book.

Our journey consists precisely of this scientific adventure that others have not bothered to embark on. We have accomplished this expedition through scientific research and extensive clinical care for patients in major university hospitals, namely, at the Beth Israel Deaconess Medical Center of Harvard Medical School, Boston, MA, and at our Research Institute for Translational Immunology at the University Medical Center in Mainz, Germany. What is protocolled in the logbook of our explorations has been published in high-ranking scientific journals in which only papers are accepted that expert colleagues classify as novel, relevant, and scientifically outstanding. We will present theses scientific results to you in

digestible and appetizing portions in the following chapters. In addition to the scientific logbook, we brought home our clinical logbook, so to speak, in which the in-depth work with our patients in the United States and in Germany is reflected. All too often, our patients are highly complicated cases that came from year-long odysseys through the medical system, where they had not found the clinical information and professional understanding that they needed. How we were able to help these patients and how the results of our research endeavors helped us to do so are what we are presenting our readers in the following chapters.

What are the unknown territories that we have charted so far? Our discoveries go far beyond what was known in nutrition and nutritional medicine. When we started, there was an exception to the well-known rule that a staple food consumed in moderation cannot cause illness, and this exception is also related to wheat: *celiac disease*. In 1997, we discovered the *celiac disease autoantigen*, published in the journal *Nature Medicine*, and thus laid the foundation to finally understand the mechanism why a common foodstuff, gluten, causes serious symptoms in celiac patients. With this discovery, we also established the urgently needed safe blood test that allowed to screen populations and detect this severe hidden disease that had been responsible for a widespread failure to thrive in infants and misery in children and adults. Because gluten is the culprit of celiac disease, many people believe or are made to believe that gluten can also be harmful to non-celiacs. This is grossly wrong, as you will learn in this book. Apart from its historical paradigm-changing role in medicine, we present celiac disease in our book in much detail, because it is still not well understood by practitioners, severely underdiagnosed in patients, and one of the most important differential diagnoses of the novel diseases we describe in the following chapters.

In this book, we present for the first time to a public outside the scientific community two novel diseases caused by defined components of wheat, other than gluten. One disease is *atypical wheat allergy* (there are also *classical wheat allergies* that are rare and have been known for some time). *Atypical allergies* are a brand new but already well-defined disease entity that was discovered by us along with our London-based friend and colleague Annette Fritscher-Ravens[1]. *Atypical wheat allergy* will be a common diagnosis in the near future. It affects predominantly the intestine and leads almost exclusively to symptoms there. Because nothing like this was known before, it has not been recognized as a form of allergy, and persons affected are usually classified as patients with “irritable bowel syndrome” (IBS), a diagnosis that, due to our discovery, will largely vanish. Besides wheat, there are other atypical allergies. Prominent are milk, soy, and yeast. Since symptoms are delayed, most patients cannot associate allergen consumption with their complaints. Our patients, in whom we have diagnosed atypical allergies with a special procedure, have all become symptom-free under the allergen-free diet. Since 10–15% of most populations worldwide have an atypical food allergy, about 60% to wheat, all healthcare systems in the world will have to realize the real cause of “IBS” because

[1] See Chap. 7.

today, it leads to immense, unnecessary costs and human suffering that can easily be avoided.

The other hitherto unknown territory that we were the first to enter on our research journey turned out to be a true continent: the continent of ATI (amylase trypsin inhibitors). Scientifically and clinically, our findings brought about a highly relevant paradigm change in the field of immunology. Our results will also change how people look at the staple food no. 1 worldwide: wheat. With the ATI, we have been able to decipher the importance of a certain class of proteins in wheat—with extremely surprising results for human health. ATI interfere with every attack and defense maneuver within the human body, making unexplainable symptoms and phenomena understandable for the first time.

However, what do ATI do? The ATI that we consume with our daily bread and wheat-based meals activate the stems and branches of innate and adaptive immunity. What these complicated mechanisms of innate and adaptive immunity mean and how they are to be understood, we will guide you through. We will show you the way through the fascinating terrain of the gut's immunology and its interaction with the entire body. What should be known already at this point: ATI heat up and worsen all diseases in which inflammatory processes play a role. We present hard data to you, showing that ATI adversely affect different classes of diseases. One class is autoimmune diseases, such as inflammatory bowel diseases, multiple sclerosis, rheumatoid arthritis, scleroderma, or lupus. Autoimmune diseases are widespread; according to the AARDA,[2] approximately 50 million Americans, 20% of the population are affected. Other diseases that are promoted by ATI are the many forms of life-threatening progressive fibrotic diseases (e.g., lung, liver, and kidney fibrosis), as well as the prevalent and grossly underestimated chronic fatigue syndrome, and even several forms of cancer. ATI are also decisive drivers of all the so-called civilization diseases that the western world and increasingly the whole world have to struggle with. Thus, we have proof that ATI contribute to obesity, metabolic syndrome, fatty liver, NASH, and type 2 diabetes. With the discovery of ATI and the understanding of the mechanisms of how they work in the human body, we have identified a vicious nutrient. If we succeed in eliminating ATI, we will have an enormous impact on world health.

Taken together, this book is about how we set foot in the newly discovered country of atypical allergies as well as the newly discovered whole continent of ATI that nobody had known about before. Join us on our journey. We can promise that you will get a completely new view of the world of nutrition and health.

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[2] American Autoimmune Related Diseases Association, Inc. (https://www.aarda.org/)

Acknowledgments by Detlef Schuppan

First, I thank all my patients whom I have seen over decades in Boston, MA, and in Mainz, Germany, and who have trusted and supported me in my explorations and scientific work, knowingly and unknowingly. Without their openness and trust, the progress that is documented in this book would not have been possible.

I am also deeply grateful to my colleagues and co-workers both in the United States and in Germany: graduate, PhD, and MD students, postdoctoral fellows, and national and international collaborators. They have been keys to a diverse, lively, and fertilizing lab, research, and clinical community, without whom, the discoveries, research, and clinical studies that are presented in this book would not have been possible. The creative synergy of these diverse contributors from more than 20 nations continues to be a fruitful ground for novel discoveries and progress. Their names are engraved in the many joint publications on wheat and food sensitivities.

I am particularly indebted to my valued colleague Prof. Annette Fritscher-Ravens, MD, who first discovered real-time food reactions in the small intestine and became my closest collaborator in the field of atypical food allergies.

We have written this book for our children, Darwin, Suldano, Renana, and Sahra, who always follow our endeavors with deep interest and tolerated our preoccupation with this work.

My greatest thanks go to my wife and coauthor, Kristin Gisbert-Schuppan, PhD. Every single part of this book is the result of our joint effort. For me, her view as a clinical psychologist, psychoanalyst, and experienced author was crucial to delve into the creative process that led to this unique book that equally addresses medical experts as well as patients. But apart from working together on this book, Kristin is an indispensable part of my entire work—as of my whole life.

Contents

About the Authors

Detlef Schuppan, MD, PhD, is director of the Institute of Translational Immunology at Mainz University Medical Center in Germany. He is also Professor of Medicine in the Division of Gastroenterology at the Beth Israel Deaconess Medical Center and Harvard Medical School in Boston, MA, USA. He made major contributions in the fields of intestinal and liver diseases, examples of which include the identification of the autoantigen of celiac disease, tissue transglutaminase; discovery of wheat amylase-trypsin inhibitors as triggers of ATI sensitivity; the new entity of atypical food allergies as a major cause of irritable bowel syndrome (IBS); key works in the diagnosis and treatment of fibrotic diseases, especially liver fibrosis and cirrhosis, to name a few. He runs a lab with numerous well-funded research projects and worldwide collaborations. His outpatient clinic is unique and currently focuses on patients with complicated and often undiagnosed food-related, intestinal, autoimmune, and liver diseases.

Kristin Gisbert-Schuppan, PhD, is a clinical psychologist, psychotherapist, and psychoanalyst. She works in private practice and at the Institute of Translational Immunology at Mainz University Medical Center in Germany. Her research focuses on narrative and psychosomatic aspects of food-related and autoimmune diseases.

Chapter 1
Introduction

The core part of this book comprises three comprehensive clinical chapters (Chaps. 4, 5, and 7) and two basic chapters (Chaps. 2 and 3). Chapter 2 provides a brief overview of the history of wheat cultivation and breeding, and of the major wheat proteins that play a causative role in the wheat sensitivities. Chapter 3 explains the anatomy of the intestine and provides an easy-to-understand description of the complex intestinal immune system, whose task is to identify food components as friend or foe. The clinical chapters broadly cover the 3 wheat sensitivities: 1. celiac disease, 2. wheat (and other food) allergies, especially the newly discovered atypical allergies, and 3. ATI sensitivity (ATI = amylase trypsin inhibitors). All three diseases cause inflammation and must, therefore, be taken seriously.

ATI-sensitivity, the centerpiece of our book (Chap. 5), is a completely novel disease entity that affects an estimated 10% of most populations. ATI sensitivity can explain many symptoms that were thought to be caused by gluten and are still sometimes discussed in public as "gluten-sensitivity". ATI are found in gluten-containing cereals, but they are a completely different class of proteins. Surprisingly, nutritional ATI exacerbate chronic diseases. These diseases are usually diseases outside the intestine. Intestinal discomfort and abdominal pain are no characteristics of ATI-sensitivity, as one might expect. Rather, ATI promote autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, and lupus, but also worsen metabolic disorders, such as obesity, type 2 diabetes and non-alcoholic steatohepatitis (NASH)—diseases of modern life. We see the striking effects of the ATI-reduced diet in the majority of our patients with these diseases. We give detailed instructions for the ATI-reduced diet in Chap. 5.

Chapter 7 deals with food allergies, with a special focus on the newly discovered *atypical food allergies*. While symptoms of *classical food allergies* are well known, they are relatively rare. They usually manifest with an immediate reaction, such as itching, sneezing, watery eyes, or severe life-threatening symptoms, like anaphylactic shock. In contrast, *atypical* wheat and other food allergies are far more frequent, affecting up to 10% of most populations, and cause mainly abdominal symptoms,

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such as bloating, pain, diarrhea, or constipation. These symptoms are remarkably similar to the symptoms of irritable bowel syndrome (IBS). In fact, most patients with IBS have an identifiable atypical food allergy, prominently to wheat, and become symptom-free once the allergen is excluded. We have developed an endoscopic technique to directly demonstrate this food allergy in the small intestine, but also describe a more practicable path to identify the allergen. In contrast to classical allergies, in atypical food allergies, it may take many hours until the symptoms become apparent. It is this insidious nature of the atypical food allergies that makes allergen identification difficult without appropriate guidance.

Apart from the novel entities, ATI-sensitivity and atypical food allergies, we devote an in-depth chapter on celiac disease (Chap. 4). Celiac disease is an outstanding example of a disease in which a defined nutrient, gluten from wheat and related cereals, causes intestinal inflammation in patients with a genetic predisposition. The term "celiac disease" is well known to a broad public, but only a few understand the underlying mechanisms and their clinical manifestations. Instead of expected abdominal symptoms like diarrhea and belly pain, most patients with celiac disease have atypical symptoms that manifest in other organs than the gut. Therefore, the majority of celiacs, up to 90%, remains undetected, even in countries with a well-developed healthcare system. The overall prevalence of celiac disease is about 1% in most populations. Once diagnosed, its treatment is straightforward: The rigorous exclusion of even traces of gluten-containing foods. Still, some patients may not improve on the gluten-free diet, since they have developed a severe form, called "refractory celiac disease", or even celiac disease-related intestinal lymphoma. With a highly reliable blood test—anti-tissue transglutaminase antibodies—most celiacs can be identified. Early diagnosis of celiac disease is particularly important for infants and children, in order to secure a normal development and prevent complications.

Due to its overrepresentation in public, we add a chapter on the so-called FODMAPs (fermentable oligo-, di-, monosaccharides, and polyols). These are natural constituents of most foods. When consumed in excess, they can cause bloating, sometimes also abdominal pain and diarrhea in some people. These effects are long known to humankind. Examples are onions, cabbage, beans, watermelon, and other fruits and vegetables. They are non-inflammatory; in contrast, they promote a healthy gut (Chaps. 5, 6, and 10). In Chap. 6 we also touch the common sugar intolerances for lactose and fructose that can cause similar symptoms as FODMAPs and are equally non-inflammatory. These intolerances are usually mild and do not justify the rigorous exclusion of foods containing lactose or fructose. Often these diagnostic labels prevent the search for the inflammatory diseases that we discuss in this book. Finally, we discuss histamine intolerance that rarely presents in a severe form and is often equally overrated.

The book concludes with a chapter in which we present the concept of our unique patient care that we have established in our outpatient clinic (Chap. 9). Thus, we carry out an in-depth exploration, which includes an extensive history taking, a meticulous study of the prior medical records, a thorough physical examination, and consideration of the patient's psycho-social context. Only after this workup, we add

missing diagnostic studies and develop a therapeutic plan. This is very time-consuming and currently not adequately reimbursed by health insurance, although it usually markedly helps the patients who are finally cured of their disease that had forced them to have numerous consultations and unnecessary tests and procedures before. Finally, our approach will lead to a dramatic reduction of healthcare costs incurred by mis- and under-diagnosis of the here described highly prevalent food-related inflammatory diseases.

All information that we provide in this book is largely based on our scientific results that have been published in the best scientific and medical journals. Selected original articles and reviews can be found in our annotated bibliography at the end of the book. Our scientific work goes hand in hand with our clinical practice. Therefore, we present individual patients and their disease and treatment process in each of the three major clinical chapters.[1] A subsequent medical commentary on every individual case helps to build an in-depth understanding of the diseases.

[1] All histories and aspects reflect true cases from our clinical practice. Nonetheless, the cases we present are completely anonymized, i.e., cases have been modified not to allow identification of the individual person.