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Unexplained thrombocytopenia, particularly with splenomegaly, should immediately raise suspicion

Q1 Your career has spanned four decades of remarkable progress in Gaucher disease (GD), from an era with no therapeutic options to one with multiple targeted therapies. What first drew you to this field?

It is indeed remarkable to realise that it is now exactly 40 years since I joined the late Ernest Beutler as a research fellow at the Scripps Research Institute, La Jolla, California, USA. Beutler was a legendary haematologist and scientist whose seminal discoveries transformed our understanding and treatment of numerous haematologic disorders. As a mentor, he taught me that the essence of being a physician-scientist is to think creatively, challenge established dogmas, and never accept consensus simply because everyone else does. These principles have guided me throughout my entire career.

My original intention was to deepen my knowledge and skills in molecular biology. I was assigned to the group working on GD shortly after they had cloned, independently and in parallel with Ed Ginns at the National Institutes of Health (NIH), the complementary DNA encoding glucocerebrosidase, the lysosomal enzyme whose inherited deficiency causes this disease. This discovery opened the molecular era of GD. This was the third major milestone in the history of GD; the first was the original description of the disease by Philippe Gaucher in 1882, and the second was Roscoe Brady's identification in 1965 of the glucocerebrosidase deficiency as the aetiology of GD.

For me, choosing GD was also quite practical. I knew that its relatively high prevalence among Ashkenazi Jews would allow me to continue studying the disease upon my return to Israel.

Importantly, when I entered the field in 1986, there was no specific treatment for GD. Patients received symptomatic treatment for pain and complications, and many severely affected patients underwent splenectomy, orthopaedic procedures, or even bone marrow transplantation. I could hardly have imagined then how dramatically this situation, and the lives of our patients, would change over the following few years.

Q2 Looking back over this time period, which milestones have had the greatest impact on the care of people living with GD?

Two key developments during my fellowship stand out, both representing milestones not only for GD but for medicine at large. The first was PCR, the revolutionary technique developed by Nobel Laureate Kary Mullis, Cetus Corporation, Berkeley, California, USA, that made it possible to amplify tiny amounts of DNA into billions of copies. In GD, PCR enabled precise molecular diagnosis and facilitated genotype–phenotype correlations, accurate prenatal diagnosis, large-scale screening, and many other advances.

The second was the development of safe and effective enzyme replacement therapy (ERT). The first clinical trial was underway at the NIH, and toward the end of my fellowship in 1989, I

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received an early indication of its success when a representative of Genzyme, Cambridge, Massachusetts, USA, approached Beutler for permission to use the glucocerebrosidase complementary DNA to develop recombinant ERT. This ultimately led to the approval of imiglucerase in 1994, 3 years after the approval of the placental-derived enzyme, and it remains the most widely used treatment for GD worldwide. Importantly, ERT's impact extended far beyond GD: its remarkable clinical and commercial success opened the door to orphan-drug development for numerous other rare diseases, benefiting patients worldwide.

Returning to Israel knowing that an effective treatment was imminent allowed me to advise patients to avoid irreversible interventions such as splenectomy or bone marrow transplantation and instead await disease-specific therapy. This contributed to the rapid expansion of our Gaucher Clinic, which within a few years became the world's largest GD centre.

Looking back, the combination of accurate molecular diagnosis and safe, effective, disease-specific therapy fundamentally transformed the lives of people with GD.

Q3 Although GD is one of the better understood lysosomal storage disorders, delays in diagnosis remain common. What are the main challenges to earlier recognition, and what should clinicians across different specialties be looking for when assessing patients with unexplained symptoms?

As with many rare diseases, the major challenge is indeed delayed diagnosis due to lack of awareness. Diagnosing GD is relatively easy once the physician remembers to consider it: from a simple dried blood spot, we can perform the whole gene sequence, measure the highly sensitive and specific biomarker glucosylsphingosine (Lyso-Gb1), and assess enzymatic activity.

GD is highly heterogeneous and multisystemic, and its individual manifestations are often non-specific. Patients may therefore present to haematologists, paediatricians, gastroenterologists, orthopaedists, rheumatologists, or other specialists and undergo extensive, sometimes invasive investigations before the correct diagnosis is made. Remarkably, one study showed that even when experienced haematologists were presented with the classic combination of anaemia, thrombocytopenia, hepatosplenomegaly, and bone pain, only 20% considered GD in the differential diagnosis.

My message to clinicians is therefore simple: think Gaucher. Unexplained thrombocytopenia, particularly with splenomegaly, should immediately raise suspicion. Other clues include anaemia, hepatomegaly, bleeding, bone pain, fractures or osteopenia, fatigue, and growth retardation in children. Hyperferritinaemia, low high-density lipoprotein (HDL), monoclonal gammopathy, or a family history of Parkinson's disease (PD) may provide additional clues. Although Ashkenazi Jewish ancestry increases suspicion, GD is pan-ethnic.

Diagnostic delays may last years, often leading to irreversible complications such as avascular necrosis of large joints, and causing pain and disability. It may also expose the patients to unnecessary invasive diagnostic procedures, such as liver biopsies, or even to unnecessary splenectomy. Another preventable tragedy is the birth of another affected sibling before the diagnosis is finally made, before even considering several of the preventive reproductive options available today.

Q4 Throughout your career, you have studied the relationship between genotype and clinical phenotype in GD. How has our understanding of this variability evolved, and what important questions about disease expression remain unanswered?

Predicting the clinical phenotype of patients with GD from mutations identified at the DNA level was a major focus of my fellowship and the subject of my GD-related publication in 1989.[1] Its clinical importance lies primarily in distinguishing non-neuronopathic GD (Type 1), for which safe and effective therapies are available, from the neuronopathic forms (Types 2 and 3), the neurological manifestations of which there are still no approved treatment for, and which may cause severe morbidity and, particularly in Type 2, early mortality.

In those early days, we had only the first two identified mutations: N370S, a 'mild' mutation, and L444P, a 'severe' one. Remarkably, these already allowed meaningful predictions: two mild mutations generally resulted in mild Type 1 disease; two severe mutations could lead to neuronopathic GD; and one of each typically resulted in more severe Type 1 disease, demonstrating that a single N370S allele provides protection against neurological involvement. I sometimes joke that with today's sequencing technology, my 3-year fellowship might have been completed in a week!

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Today, more than 800 *GBA1* variants have been identified, creating a very different challenge. Increasingly, genetic testing identifies previously uncharacterised variants whose clinical significance is uncertain. When two such rare variants are detected, one in each parent-to-be, predicting whether they are disease-causing and what phenotype they might produce can remain difficult, limiting our ability to provide patients and families with truly informative genetic counselling.

Q5 You have led clinical trials evaluating enzyme replacement therapy, substrate reduction therapy (SRT), pharmacological chaperones, and other novel treatments. Looking back, which therapeutic advances have most fundamentally changed outcomes for people living with Gaucher disease?

Having a large number of patients at a single referral centre provides a major advantage for drug development, particularly in rare diseases, where access to eligible patients is often critical to successful clinical trials. We have been privileged to participate in most GD trials conducted to date, with notable exceptions being the seminal successful trial of placental-derived ERT and an early trial of isofagomine, the first pharmacological chaperone, which ultimately failed.

Our large patient population has even enabled us to conduct FDA-guided, single-centre trials. These included the Phase I/II study of the first gene-activated recombinant ERT produced in a human cell line by *TKT*, velaglucerase alfa, and an earlier Phase II maintenance study of miglustat, the first oral SRT. The rationale was simple: even if miglustat was less effective than intravenous ERT in reversing disease manifestations, perhaps it could maintain the improvements already achieved with ERT.

As to which therapeutic advance most fundamentally changed outcomes, the answer is unequivocal: the original ERT and its recombinant successors. Remarkably, unlike many areas of medicine where successive generations of therapies steadily improve outcomes, no subsequent GD therapy has proven more effective or safer than the original placental-derived ERT introduced in 1991. Moreover, what ERT could not address remains a major unmet need despite newer ERTs, oral SRTs, and ongoing development of novel approaches, including gene therapy.

Q6 How have treatment goals evolved as new options have become available?

First, I would like to put the concept of therapeutic goals in GD into perspective. Formal therapeutic goals are not defined for most diseases; rather, clinical guidelines generally establish specific treatment targets, such as glycaemic control in diabetes or blood-pressure targets in hypertension.

GD is somewhat unusual in having formally defined therapeutic goals for haematologic, visceral, skeletal, and quality-of-life outcomes. In my view, these goals are better regarded as expected responses to ERT rather than as universal definitions of optimal treatment outcomes. Fortunately, to the best of my knowledge, these formal therapeutic goals are not routinely used in any of the major GD referral centres.

Ultimately, our ambitions for patients should extend well beyond meeting predefined numerical targets. We should strive for normalisation, or the greatest possible improvement, of disease manifestations; prevention of irreversible complications and GD-associated comorbidities; and, above all, the best possible long-term health and quality of life.

Q7 Research is now moving beyond established therapies towards gene therapy, oral enzyme replacement, and other innovative approaches. Which emerging treatments do you believe have the greatest potential to transform the future management of GD?

Gene therapy might well become the ultimate therapeutic modality for patients with GD: a single administration that could provide a lifelong supply of normal glucocerebrosidase from the patient's own cells. However, this extraordinary promise must be balanced against uncertainties regarding long-term safety, durability, and efficacy. In GD, particularly Type 1, we already have highly effective and remarkably safe treatments. It may therefore be more appropriate for gene therapy to demonstrate its transformative potential first in severe, life-threatening genetic diseases for which no effective treatment currently exists. As experience accumulates and the technology becomes safer, more predictable, and demonstrably durable, gene therapy could assume an increasingly important role in GD and perhaps ultimately transform its management, fulfilling the long-held aspiration of replacing lifelong therapy with a single therapeutic intervention.

That said, our Gaucher Unit at Shaare Zedek Medical Center, Jerusalem, Israel, is participating in a Phase III gene-therapy trial and recruiting carefully selected, highly motivated patients. One rationale for participation is that regulatory approval, if ultimately achieved, does not necessarily guarantee reimbursement or timely access in every country. For some patients, participation in an advanced Phase III trial therefore represents an opportunity to gain early access to a potentially transformative therapy, while contributing to the evidence needed to establish its long-term safety, efficacy, and durability.

Q8 One of the most significant discoveries in the field has been the association between *GBA* variants and PD. How has this changed our understanding of GD, and what opportunities does it present for improving the diagnosis, monitoring, and potential prevention of PD?

Of the more than 370 papers I have published, I consider our 1996 report[2] describing the association between GD and PD my most important contribution. Our original six patients shared a distinctive phenotype: earlier-onset, more severe PD, relatively mild GD, and prominent cognitive impairment, features now well recognised in *GBA1*-associated PD. *GBA1* variants are, in fact, the most important genetic risk factor for PD, and *GBA1*-PD is increasingly recognised as a distinct clinical and pathobiological entity.

We prefer the name Sidransky syndrome, honouring Ellen Sidransky, whose pioneering work established this remarkable connection and helped open an entirely new field of research and drug development.

I believe this association has taught us more about PD than about GD. In my view, PD is a comorbidity of GD rather than another manifestation of its metabolic defect. Importantly, I believe the key mechanism is not simply loss of glucocerebrosidase activity (loss of function), but the consequences of mutant glucocerebrosidase misfolding, endoplasmic reticulum stress, and impaired proteostasis, ultimately promoting α-synuclein accumulation and dopaminergic neurodegeneration (gain of function). This distinction is not merely academic; it determines how we design therapies. Our concern about substrate reduction as a strategy was raised years ago, before its subsequent clinical failure.

Ultimately, if a safe disease-modifying therapy becomes available, identifying at-risk *GBA1* carriers during the prodromal, pre-motor phase could offer the extraordinary possibility of preventing PD before it develops.

Q9 As founder of one of the world's largest GD referral centres, you have cared for hundreds of patients over many years. What have you learned about the value of long-term follow-up and multidisciplinary care, and how can these lessons be applied to other rare diseases?

We are living in an era when there is considerable discussion about whether AI may replace some of what doctors currently do. This may be true for specific tasks, such as interpreting imaging or pathology, summarising medical records, suggesting differential diagnoses, or checking drug interactions. However, AI is unlikely to replace the comprehensive,

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> **AI is unlikely to replace the comprehensive, longitudinal care required for patients with rare diseases**

longitudinal care required for patients with rare diseases. GD is an excellent example. It is a multisystem genetic disorder with extraordinary phenotypic heterogeneity. At one end of the spectrum are asymptomatic or very mildly affected individuals who may require little more than periodic follow-up; at the other are infants with severe manifestations, including hydrops fetalis, for whom specific therapy may offer little benefit and where genetic counselling and prevention of recurrence become particularly important. Long-term follow-up allows us to understand the natural history of the individual patient and, importantly, to distinguish Gaucher-related manifestations from unrelated comorbidities or treatment-related complications. An unexpected change in a patient's clinical course or response to treatment should prompt us to look for another explanation. This is also why multidisciplinary care in an experienced referral centre is so valuable. Specialists in orthopaedics, haematology, neurology, hepatology, gynaecology, genetics, and other disciplines develop specific expertise in managing these patients throughout their lives. With the increasing number of therapeutic options, individualised clinical judgement becomes even more important. GD therefore provides a model for other rare diseases: centres of excellence should combine long-term follow-up, multidisciplinary expertise, genetic counselling, and individualised treatment. AI will undoubtedly become an increasingly valuable tool, but it should complement rather than replace the experienced physician who knows both the disease and the patient.

Q10 GD has often been cited as a model for successful rare disease drug development. What factors enabled the field to progress so rapidly, and what lessons could researchers working on other rare diseases take from this experience?

GD is indeed a remarkable success story in rare disease drug development. Several factors contributed to this progress. Early identification of the underlying enzymatic defect provided a clear therapeutic target and ultimately led to ERT, transforming GD from a potentially debilitating disorder into a treatable condition, accompanied, as mentioned earlier, by remarkable commercial success.

Close collaboration between basic scientists, clinicians, patients, and industry was equally important. Although GD is rare and highly heterogeneous, its ethnic predilection provided a unique advantage. Among Ashkenazi Jews, GD is relatively common (~1:800), and the concentration of a large number of patients in several academic centres facilitated both basic research and clinical development. Moreover, most patients have Type 1 GD, without primary neurological involvement or severe deformities, and may have a near-normal lifespan even without treatment, making the disease particularly suitable for long-term therapeutic development.

Another advantage is the availability of objective, easily measurable outcome parameters, including spleen and liver size, blood counts, and biochemical parameters, complemented by sensitive disease-specific biomarkers. Success stimulated further innovation, from several ERTs to oral SRT, pharmacological chaperones, and experimental gene therapies.

The broader lesson is that successful rare disease drug development requires more than a promising drug: it requires an understanding of disease biology, well-characterised patient cohorts, reliable biomarkers, centres of excellence, long-term registries, and international collaboration. Nevertheless, important unmet needs remain, particularly neuronopathic GD, access to therapy in poorer countries, and the challenges of comorbidities such as certain malignancies and PD.

Q11 Over the course of your career, you have been involved in the development and evaluation of ERTs, SRTs, and pharmacological chaperones. As treatment options continue to expand, how do you approach selecting the most appropriate therapy for different patients, and is the field moving towards truly personalised treatment strategies?

The increasing number of therapeutic options in GD is certainly good news, but it also makes treatment decisions more complex. Treatment should be tailored to the individual patient rather than simply to the diagnosis.

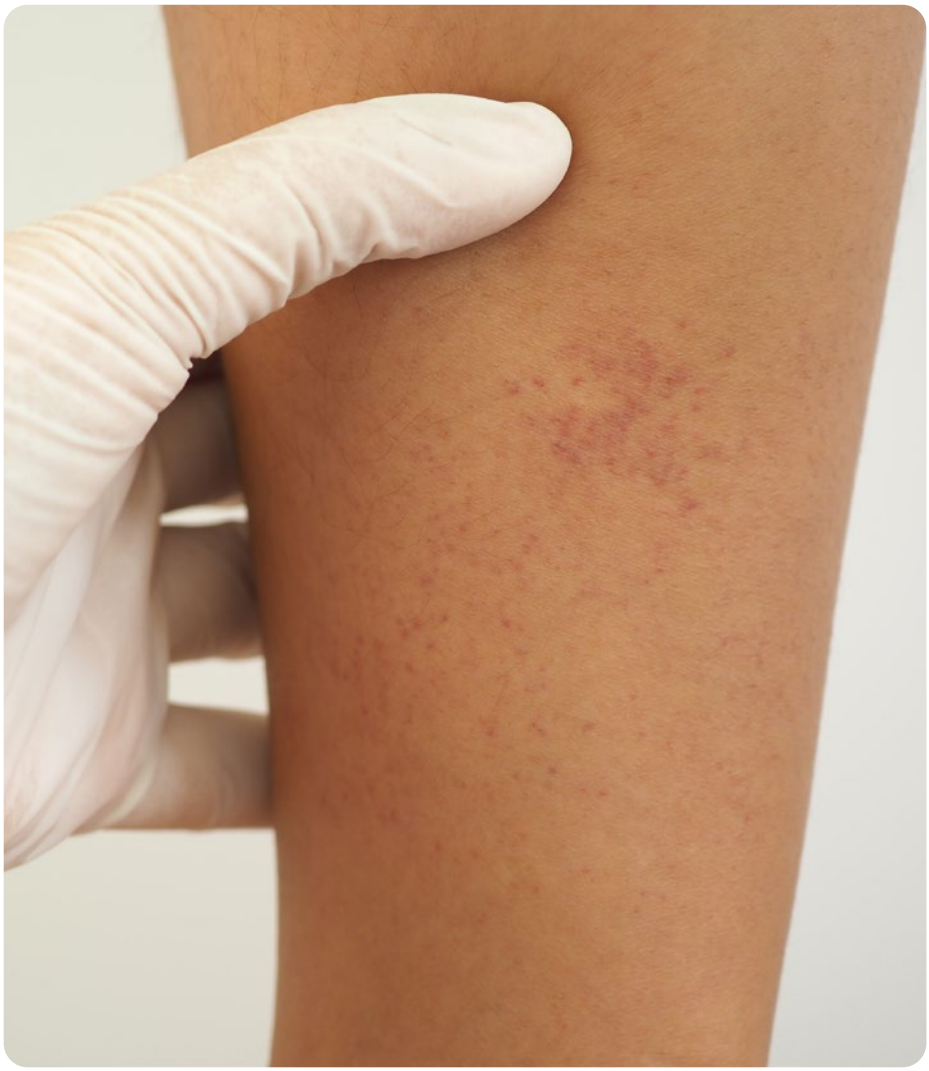
For Type 1 GD, I still consider ERT the standard first-line therapy, based on its efficacy, safety, and more than three decades of experience. Although available

ERTs are similar, differences in immunogenicity, hypersensitivity reactions, administration, and cost may influence individual choice. Oral SRT may be attractive, particularly for patients unwilling or unable to receive intravenous therapy, but age, comorbidities, concomitant medications, drug interactions, and compliance must be considered.

Personalisation also means recognising that not every patient requires treatment. Mildly affected patients may need only careful follow-up, whereas severe systemic disease requires early intervention. Neurological involvement presents a particular challenge because conventional ERT does not cross the blood–brain barrier (BBB).

Investigational approaches such as the pharmacological chaperone high-dose ambroxol and brain-penetrant SRTs such as venglustat are therefore of particular interest.

True personalised medicine should integrate genotype, phenotype, biomarkers, comorbidities, previous treatment response, and, importantly, patients' preferences and lifestyle. In reality, however, GD remains rare, making head-to-head trials of different therapeutic modalities unlikely. Moreover, cost and reimbursement remain major considerations in many countries. Consequently, treatment decisions are often influenced not only by what is optimal for the individual patient, but also by where the patient lives and the restrictions imposed by local healthcare systems. Nevertheless, the expanding therapeutic toolbox should increasingly allow us to select the right treatment, or sometimes no treatment, for the right patient at the right time.



Q12 Despite major therapeutic advances, what do you consider to be the greatest unmet needs for people living with GD today, and where should future research efforts be focused?

Despite the remarkable success of ERT and SRT, major unmet needs remain. The greatest is undoubtedly neuronopathic GD. ERT has dramatically improved the systemic manifestations of Type 3 GD, but it does not cross the BBB and therefore does not prevent progressive neurological disease. Developing safe therapies that reach the brain should therefore remain a major research priority.

A second challenge is preventing long-term complications that are not adequately addressed by current therapies. These include PD and haematological malignancies, particularly multiple myeloma. Understanding why these complications occur, identifying patients at the greatest risk, and developing preventive strategies are important goals for the next generation of research. Indeed, current ERTs and SRTs have not been shown to eliminate these GD-related comorbidities.

> **GD is indeed a remarkable success story in rare disease drug development**

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We also need better biomarkers and predictors of disease progression at the pre-symptomatic stage. Earlier diagnosis is important because delayed treatment can result in irreversible, particularly skeletal, complications; conversely, increasingly early diagnosis through genetic or newborn screening creates the problem of determining who actually needs treatment and when to start it.

Finally, perhaps the most troubling unmet need is global access. We have highly effective but extremely expensive treatments that remain unavailable to many patients in poorer countries. Scientific progress should therefore be measured not only by developing better therapies, but also by ensuring that effective treatments reach the patients who need them.

Q13 Finally, looking ahead, what developments in GD research are you most hopeful about, and what advice would you give to clinicians and researchers entering the field?

Looking ahead, I try to combine optimism with realism. Gene therapy is enormously exciting and has attracted considerable scientific and financial expectations, but we are still at a very early stage. Important questions remain regarding safety, durability of gene expression, and, ultimately, whether these approaches will provide meaningful lifelong clinical benefit. I therefore believe that a more immediate and realistic hope is the development of an effective pharmacological chaperone that combines the safety and efficacy we have achieved with ERT with the ability to cross the BBB. Such a therapy could address the major unmet need of neuronopathic GD and, potentially, reduce the risk of *GBA1*-associated PD. High-dose ambroxol provides encouraging proof of concept, although definitive controlled trials are still required, and a second generation with an even better BBB penetrance and possibly a single lower dose should be developed.

My advice to young clinicians and researchers is first to acquire deep knowledge of the disease. AI will become an extraordinary tool, but you need sufficient expertise to recognise whether the answers it provides are correct. For clinicians, nothing replaces listening carefully to patients and learning from them.

I would also encourage young colleagues to visit centres in different countries and populations. GD in Egypt may look different from that in the UK, and patients in Pakistan may differ from those in Japan. International collaboration, including telemedicine and focused working groups, can teach us an enormous amount.

Finally, remain independent and intellectually honest. Question consensus statements, understand who produced them, and avoid allowing relationships with industry to influence scientific judgement. Above all, remain curious, dedicated, and enthusiastic.

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