THE CLINICAL DEVELOPMENT OF THE SOMATOSTATIN ANALOGUE OCTREOTIDE

Alan G. Harris

The Clinical Development of
the Somatostatin Analogue Octreotide

Alan G. Harris
Thesis, Erasmus University, Rotterdam, Department of Internal Medicine
with references, summary in English and Dutch

Front cover: *Le Pont de Langlois à Arles*, Vincent Van Gogh, 1888.
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THE CLINICAL DEVELOPMENT OF THE SOMATOSTATIN ANALOGUE OCTREOTIDE

DE KLINISCHE ONTWIKKELING
VAN DE SOMATOSTATINE ANALOOG OCTREOTIDE

THESIS

To obtain the degree of doctor from the Erasmus University Rotterdam
on the authority of the Rector Magnificus Prof. dr. ir. J.H. van Bemmel
according to the decision of the Doctoral Board.

The public defence shall be held on
Friday, 24th January 2003 at 11.00 hours

by

Alan Gerald Harris
Born in Dublin (Ireland)

DOCTORAL COMMITTEE

Supervisor:	Prof. dr. S.W.J. Lamberts
Other members:	Prof. dr. G.J. Bruining
	Prof. dr. E.P. Krenning
	Prof. dr. J.A. Romijn

DE KLINISCHE ONTWIKKELING VAN DE SOMATOSTATINE ANALOOG OCTREOTIDE

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PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus Prof. dr. ir. J.H. van Bemmel
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden
op vrijdag 24 januari 2003 om 11.00 uur

door

Alan Gerald Harris
Geboren te Dublin (Ireland)

PROMOTIE COMMISSIE

Promotor:	Prof. dr. S.W.J. Lamberts
Overige Ieden:	Prof. dr. G.J. Bruining
	Prof. dr. E.P. Krenning
	Prof. dr. J.A. Romijn

To my parents,
In memoriam

To my brother David,
With love

Science sans conscience n'est que ruine de l'âme
François Rabelais

The joy of discovery is certainly the liveliest that the mind of man can ever feel
Claude Bernard

ABBREVIATIONS

5-HT	5-hydroxytryptamine
ACE	Angiotensin converting enzyme
ACTH	Adrenocorticotropic hormone
AGE	Advanced glycosylation end products
AIDS	Acquired immune deficiency syndrome
AR	Aldose reductase
AUC	Area under the curve
CCK	Cholecystokinin
CPMP	Committee for Proprietary Medicinal Products
CT	Computerised tomography
DCCT	Diabetes Control and Complications Trial
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
EGF	Epithelial growth factor
EMEA	European Medicinal Evaluation Agency
ERCP	Endoscopic retrograde cholangiopancreatography
EU	European Union
FDA	Food and Drug Administration
FT4	Free thyroxine
GCP	Good Clinical Practice
GEP	Gastroenteropancreatic endocrine tumours
GFR	Glomerular filtration rate
GH	Growth hormone
GHRH	Growth hormone releasing hormone
HbA1c	Haemoglobin A1c (glycosylated haemoglobin)
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HREC	Human retinal endothelial cells
IGF-1	Insulin-like growth factor-1
IGFBP	Insulin-like growth factor binding protein
LAR	Long acting repeatable
LDL	Low density lipoprotein
MRI	Magnetic resonance imaging
mRNA	(messenger) Ribonucleic acid
NIH	National Institutes of Health
NMR	Nuclear magnetic resonance
OGTT	Oral glucose tolerance test
OSAS	Obstructive sleep apnoea syndrome
PCR	Polymerase Chain Reaction
PRGC	Percentage relative gallbladder contractility
RPF	Renal plasma flow
SD	Standard deviation
SEM	Standard error of the mean
SR	Slow release
SRIF	Somatotropin Release Inhibitory Factor
SSTR	Somatostatin receptor subtype
TGFβ	Transforming growth factor beta
TNF-α	Tumor necrosis factor alpha
TPN	Total parenteral nutrition
TRH	Thyrotropin releasing hormone
TSH	Thyroid stimulating hormone
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
VIP	Vasoactive intestinal polypeptide

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EMEA	European Medicinal Evaluation Agency
ERCP	Endoscopic retrograde cholangiopancreatography
EU	European Union
FDA	Food and Drug Administration
FT4	Free thyroxine
GCP	Good Clinical Practice
GEP	Gastroenteropancreatic endocrine tumours
GFR	Glomerular filtration rate
GH	Growth hormone
GHRH	Growth hormone releasing hormone
HbA1c	Haemoglobin A1c (glycosylated haemoglobin)
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HREC	Human retinal endothelial cells
IGF-1	Insulin-like growth factor-1
IGFBP	Insulin-like growth factor binding protein
LAR	Long acting repeatable
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MRI	Magnetic resonance imaging
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Chapter I.

General Introduction and Aims of Thesis

I.I - GENERAL INTRODUCTION

This thesis provides an overview of the clinical development of the somatostatin analogue, octreotide, from my viewpoint as the coordinator/developer of the Clinical Development Program at Sandoz*. The thesis describes in detail the rationales that governed the direction and speed of the various branches of the research program, and the unique methods by which data were collected and registration was sought are outlined.

The main theme of the thesis is how close cooperation between industry and academia for the study and development of a new pharmacological agent can be mutually beneficial. Academic groups receive economic and structural support from the industrial sector, thereby increasing knowledge regarding pathophysiological mechanisms. Industry, on the other hand, is rewarded with valuable information concerning the utility and hazards of the potential pharmacotherapy being studied. The clinical development of octreotide has not only produced a potent and well tolerated medication for the treatment of numerous conditions, it has also broadened significantly our understanding of many disease mechanisms and has proven singularly successful as a commercial drug.

When dealing with the treatment of relatively rare diseases such as acromegaly and gut endocrine tumours, one of the most significant obstacles encountered is that of the scattering of patients across national and international boundaries. Data collection from such patients represents a significant hurdle for the individual academic investigator; however, during the clinical phase of octreotide's development we showed that a multinational pharmaceutical company working together with individual clinical research groups could compile successfully data of the highest quality. It attests to the effectiveness of this process that octreotide was approved rapidly in many countries worldwide based in major part on these collections of patient data.

The successful clinical development of octreotide revolutionised the treatment of gut endocrine tumours, giving back dignity, mobility and a significantly improved quality of life to those suffering from this debilitating illness. Had the benefits ended there, octreotide would have earned the appellation of a "breakthrough medicine". However, with this somatostatin analogue, a new chapter has also been opened in the treatment of acromegaly, affording hope to those patients who were unresponsive or could not avail themselves of pre-existing therapies. Moreover, by maintaining close links with the premier academic institutions worldwide, other potentially valuable avenues of clinical research were pursued. Indeed, as noted by Guillemin, "these early observations (regarding somatostatin physiology) would become of practical clinical significance and application only if and when taken up by industry"[1]. Good evidence regarding octreotide continues to accumulate, pointing to its use in the treatment of such major problems as variceal bleeding, secretory diarrhoea, short bowel syndrome, fistulae, diabetic retinopathy, diabetic nephropathy and cancer.

I.II - AIMS OF THE THESIS

The thesis begins with an encapsulated history of the discovery of somatostatin and the launching of the somatostatin analogue program (Chapter II). This is followed by a brief description of the design and preclinical development of octreotide and the original conception of the Clinical Development Program, including Phase I to Phase IV, beginning with the emergence of octreotide in 1982. The underlying motives for using octreotide as a clinical agent are

* The corporate entity Sandoz is now known as Novartis

highlighted, which involves tracing briefly the physiological actions of somatostatin, in addition to explaining the pathological basis of the diseases chosen for treatment. Furthermore, the rationales involved in the design of the Clinical Development Program are discussed, as are the decisions underlying the specific clinical goals pursued. This provides an insight into the expectations held at the early stages of development, and relates these hopes to the final results. Where insurmountable problems were encountered, the effects of these problems on the progression of research into specific therapeutic goals are outlined. Our approach to the prioritisation and sequencing of research goals changed as the program progressed. This was due to the impact of new external research findings and the results gained from the trials related to the Clinical Development Program. In reality the Clinical Development Program for octreotide followed a process of evolution and adaptation, rather than sequential steps.

Separate sections of the thesis are given over to dealing with the development of octreotide in the initial primary indication, diabetes mellitus (Chapter III), followed by acromegaly (Chapter IV), gut endocrine tumours and gastroenterological conditions (fistulae, AIDS-related diarrhoea, and variceal bleeding) (Chapter V). A separate section details a number of the miscellaneous clinical applications of octreotide (Chapter VI). The anticipated side effects resulting from the known physiological and pharmacological effects of native somatostatin and of octreotide have always been highlighted and studied in a pro-active way. Indeed, the manner in which octreotide was developed facilitated the free and frank discussion of the nature of these side effects and encouraged research into the mechanisms that underlie them. This topic is discussed in the light of clinical data derived from the development program (Chapter VII). As industry moves further into the realm of "high tech" pharmaceuticals, the lessons learned during the development of octreotide in rare conditions have particular relevance. In the Discussion section (Chapter VIII), our experiences during the Clinical Development Program for octreotide are put into context and recommendations for other pharmaceutical researchers are detailed. This includes how opportunities for unexpected developments can be leveraged, such as, the advent of somatostatin receptor imaging and radiotherapy developed at Erasmus Medical Centre, Rotterdam. Chapter VIII emphasizes how a dynamic approach to data gathering and research can be successful if it is backed by goodwill and cooperation from key academic leaders. Chapter IX relates new advances in clinical research tools - particularly genomics and proteomics - and somatostatin physiology to the possibilities for future research with octreotide and the potential for newer analogues. Finally, conclusions are presented in Chapter X.

References

1. Guillemin R. Somatostatin: the early days. Metabolism. 1992; 41(9 Suppl 2): 2-4.

Chapter II.

From Somatostatin to Octreotide

II.I - CHARACTERISTICS OF SOMATOSTATIN

Octreotide is a synthetic analogue of the naturally occurring hormone, somatostatin. Somatostatin was discovered by Guillemin and his co-workers following an observation by Krulich and Dhariwal in McCann's laboratory in 1968 that growth hormone (GH) secretion from the pituitary gland could be stimulated and inhibited by crude extracts of another closely related structure, the hypothalamus [1]. In the following year, Hellmar and Lernmark noted that pancreatic insulin secretion could be inhibited in vitro by an unknown agent present in pancreatic extracts [2]. In early 1973, Brazeau, a post-doctoral member of Guillemin's research team, under the supervision of the group's physiologist, Wylie Vale, made the serendipitous discovery of a hypothalamic factor that inhibited GH secretion which Guillemin termed somatotropin release inhibitory factor (SRIF), or somatostatin [3]. The primary somatostatin sequence was isolated by Roger Burgos, confirmed by Nicholas Ling using mass spectroscopy, following which Jean Rivier chemically synthesised a replicate sequence identical to somatostatin. In his historical review of this important period [4], Guillemin noted the importance to this work of Berson and Yalow's development of the radioimmunoassay for GH (for which Yalow received the Nobel Prize for Medicine or Physiology), and also the development by Wylie Vale of a bioassay for hypophysiotropic factors.

Somatostatin was noted to be a small 14 amino acid peptide (tetradecapeptide). The native molecule was found to have a cyclic structure, joined by two intramolecular disulphide cysteine bonds, however the linear derivative was found to have identical biological activity. A second form of somatostatin, termed somatostatin-28 was discovered in 1980 [5]. Later, in 1977, Guillemin was awarded the Nobel Prize for Medicine based on his work on the hypothalamic-pituitary axis, including the discovery of somatostatin.

In the period since its discovery, somatostatin has been shown to be present in many other tissues, including the D-cells of the pancreas, the lining of the gut and peripheral nervous system [6,7,8]. Somatostatin is remarkable also for its quite strict conservation throughout different species [9]. This so-called phylogenetic conservation gives an intimation of the central importance of somatostatin in the regulation of many physiological functions (*Figure 1*). Great developments in the field of somatostatin receptor research have been made over the past number of years. Five somatostatin receptor subtypes, all of which belong to the G-protein family of receptors, with seven membrane-spanning areas, have been characterised by Reisine, Bell and others [10,11]. These receptors are distributed throughout many tissues, especially on endocrine active cells. The binding characteristics of somatostatin to each somatostatin receptor subtype are different, indicating a variation in functions subserved by each subtype across various organ systems. For example, the main receptor sub-populations found in pituitary adenomas are types 1, 2 and 5 [12], and the expression of receptor populations may vary with cell characteristics [13]. Since these receptors are known to be functional, their presence probably plays a major role in the regulation activity of these cells in both health and disease.

Given the wide distribution of somatostatin and its receptors throughout the body and somatostatin's varied mechanisms of action, it is not surprising that it has numerous physiological functions. In general, however, somatostatin has two important regulatory roles: (a) the inhibition of brain and gut hormone release and (b) the regulation of gastrointestinal absorption and motility. Other important functions, such as an involvement in the immune system [14], are not yet fully understood and are the subject of a great deal of research.

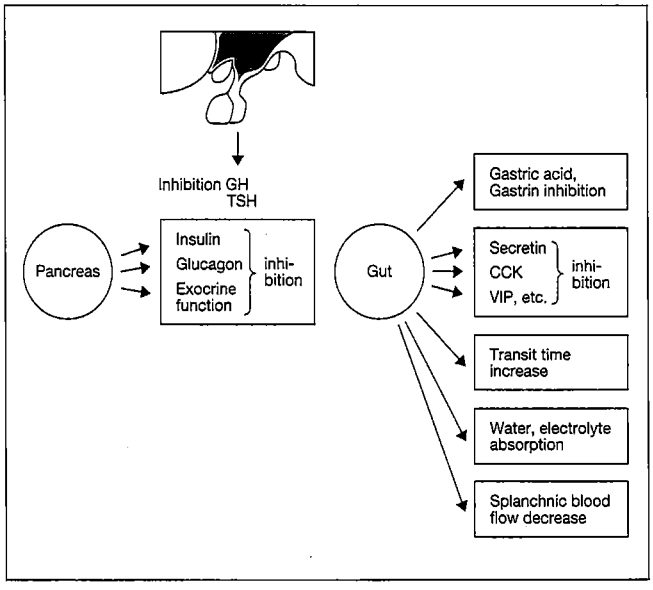

Figure 1. Physiological functions of somatostatin in human.

II.II - THE ADVENT OF SOMATOSTATIN ANALOGUES

Somatostatin's role as a GH inhibitor provided an immediately apparent rationale for its use as a therapeutic agent, namely in the treatment of disorders associated with hypersecretion of GH or gastrointestinal and/or pancreatic hormones as well as disorders of gut absorption and motility. Although several such diseases exist, somatostatin has not become a standard therapy in their treatment for two crucial reasons, 1) its biological half-life, and 2), the non-specific nature of somatostatin's inhibitory effects on GH and insulin. Somatostatin has a very short plasma half-life (2.5 minutes) and is associated with rebound hypersecretion of hormones such as GH and glucagon when treatment is halted [15]. Somatostatin also suppresses the secretion of insulin and GH to approximately the same extent, thereby increasing the risk of disturbed glycaemic control. Therefore, somatostatin is unsuitable as a treatment to reduce GH secretion over the long term, particularly in conditions where glycaemic control is important, such as diabetes mellitus. For this reason, a number of long-acting somatostatin analogues were developed, octreotide (SMS 201-995, Sandostatin®) [16], lanreotide (BIM-23104, Somatuline®) [17], vapreotide (RC-160) [18] and an early unsuccessful hexapeptide analogue, MK-678 [19]. For comparative purposes, the absolute stereochemical structures of somatostatin and these peptide analogues are reproduced for this thesis in Appendix 1.

Drug Design

The development of octreotide by Sandoz began immediately after the publication of Brazeau and Guillemin's discovery of somatostatin in the journal, Science [3] (*Figure 2*). In 1974, Sandoz formed the "SRIF-Project" team, involving six laboratory units in chemistry and biology, under the direction of J Pless, to produce long-acting synthetic analogues of somatostatin. Sandoz had a history of vibrant research interest in pituitary hormones, both anterior and posterior. During the next five years full size "peptide" analogues were designed but this did not generate any useful leads until 1978 when Jean Rivier, Wylie Vale and Nicholas Ling from the Salk Institute, La Jolla, California, as part of their effort to identify the minimal "essential" sequence of SRIF, synthesised several analogues of "reduced size" (oligosomatostatins). The overall conclusion of this work brought about the conclusion that the sequence of phenylalanine at position 7 and threonine in 10 was essential for biological activity [20]. Based on these collected findings, Sandoz directed its efforts to the "mini-SRIF" project, which synthesised highly potent analogues of reduced size by incorporating additional structural elements into the "minimal essential sequence". The Phe7-Thr10 sequence was stabilised by cyclisisation with a cysteine bridge. Physical and computer-assisted modelling were used and culminated in the selection of compound 9, termed "SMS-201-995", for further development [16]. The introduction of two non-natural amino acids, D-Phe at the N-terminal and L-Thr-ol at the C-terminal and substitution of L-Trp by its D-isomer made this octapeptide highly resistant to enzymatic degradation thus increasing its half-life dramatically and enhancing its biological potency. The final synthetic process which was developed by J. Pless and W. Bauer in conjunction with T. Petcher, P. Marbach and W. Doepfner and their colleagues was impressive, involving 25 separate steps, in which neither intermediates nor octreotide itself were crystallisable, yet this process yielded a 98% pure peptide in industrial amounts [16]. The structures of somatostatin and octreotide are depicted in Figure 3. The criteria applied by the Sandoz Preclinical Research department to putative somatostatin analogues were that the analogue should have increased resistance to enzymatic attack and greater biological potency than native somatostatin. Moreover, it should inhibit GH more selectively than insulin and display a longer duration of action than somatostatin. Octreotide had a biological half-life of the order of 90 minutes and was also relatively more potent in the inhibition of GH and glucagon than insulin, compared with somatostatin itself, in animals [16]. The development of a specific radioimmunoassay for octreotide helped immensely in the modelling of the pharmacological profile of octreotide during early stages of preclinical and clinical research.

The driving force from a therapeutic standpoint was the theory that GH suppression could either prevent or reduce the late complications of poorly controlled diabetes mellitus, such as diabetic retinopathy. It was felt that the synthesis of octreotide could represent an effective means of suppressing GH secretion in diabetic patients. Before embarking on treatment of patients, pharmacological studies were performed in animals and humans. These studies investigated both the pharmacokinetics of subcutaneous and intravenous administration and the pharmacodynamic effects of octreotide on GH, insulin and glucagons, as these were the prototypical endpoints for the investigation of safety and efficacy in somatostatin research.

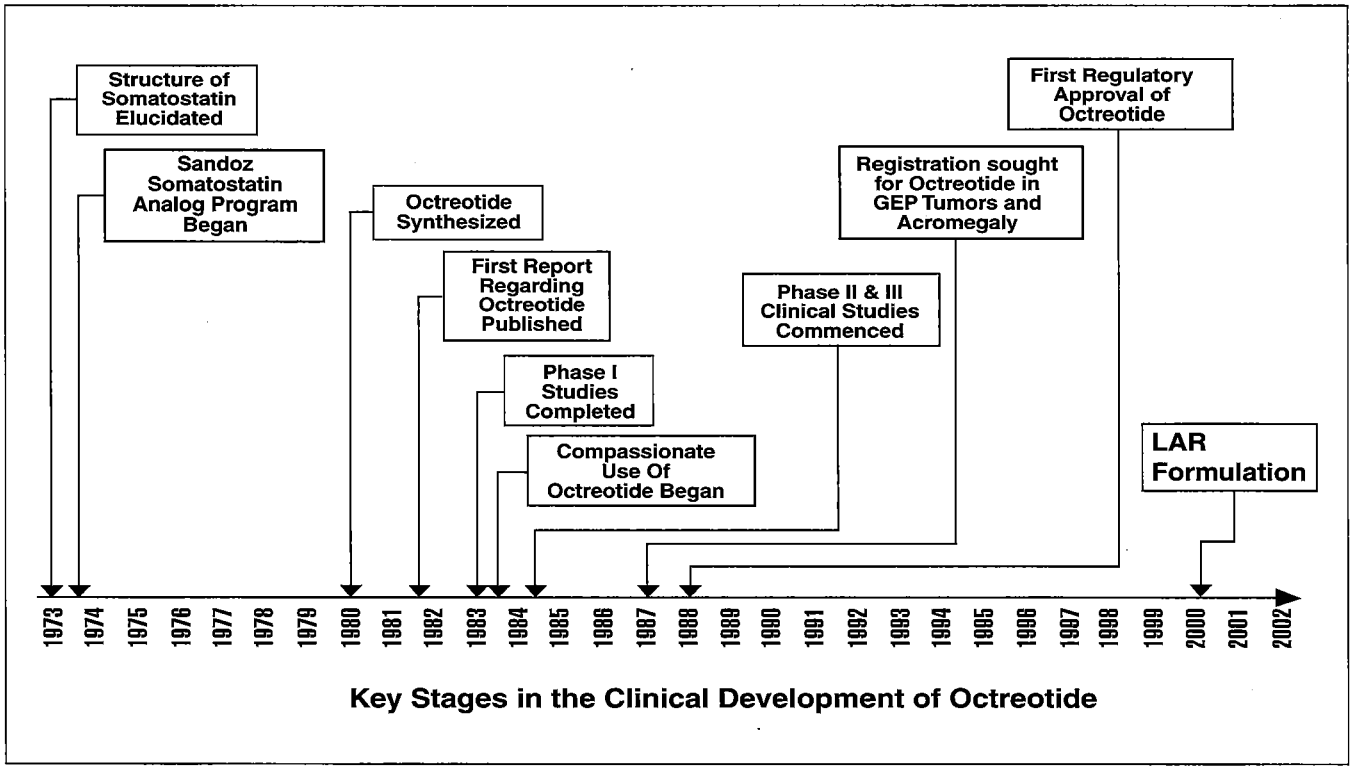

Figure 2. Chronology of the discovery of somatostatin and the clinical development of octreotide. LAR = Long acting repeatable formulation of octreotide.

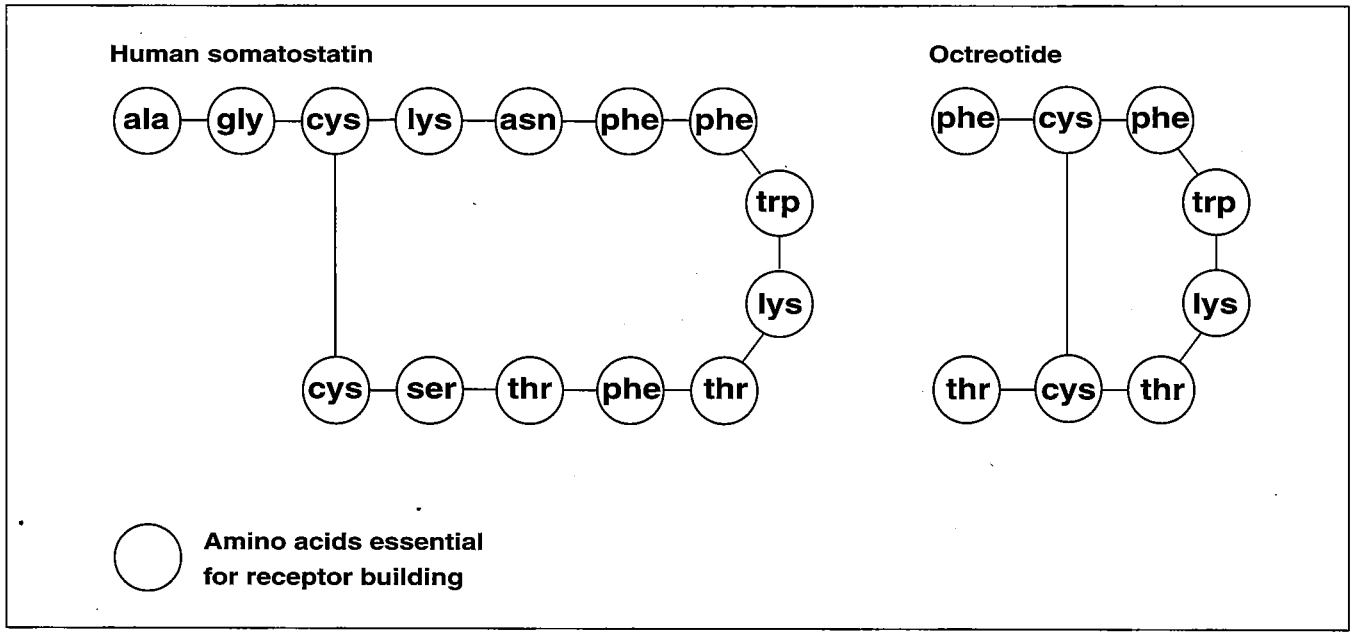

Figure 3. The amino acid structures of somatostatin and octreotide.

II.III - PRECLINICAL AND CLINICAL DEVELOPMENT OF OCTREOTIDE

Drug development is classically divided into separate phases, during which specific types of research are performed to yield necessary information about the characteristics, pharmacology, safety and efficacy of the potential drug compound *(Figure 4)*. The process of drug discovery, development and design involves investigative research in vitro and in animal models, followed by a process of careful clinical trials for appropriate candidate drugs. After the successful development of a new pharmaceutical, assessments are made post-launch regarding how the new product compares with others, and new indications are sought for the drug in the future. During the development process many important regulatory requirements have to be satisfied, starting with a tight definition of the proposed use of the drug in addition to the formulation of the drug and the proposed dose. Quality issues are also to the forefront, as requirements regarding manufacturing including dosage, impurities, stability and additives must be strictly adhered to. Early studies must provide information on how the body handles the drug metabolically, which involves the performance of ADME studies (absorption, distribution, metabolism, excretion). These studies are accompanied by early safety analyses in animal models to assess safety and toxicity in terms of carcinogenesis, damage to gametes and potential teratogenicity. Preclinical testing is performed in vitro, in vivo and increasingly in computer simulations (so-called in silico). Phase I trials are the first studies in humans and the pharmacological and metabolic properties of the drug are tested rigorously in small numbers of healthy adult volunteers to determine tolerability, early safety, pharmacokinetics and pharmacodynamics using surrogate biological markers of the target disease (e.g. growth hormone and acromegaly). Phase II studies represent the first time a potential drug is used in a patient population, and pharmacological, efficacy and safety data are collected regarding the drug across a range of possible doses. Based on the results of the phase II studies in a limited number of patients demonstrably safe and potentially useful compounds may go forward into phase III studies, which are formal therapeutic, randomised controlled trials performed in hundreds or thousands of patients to determine the safety and efficacy of the drug. Variability in drug response is performed in phases II and III. Phase III is a rigorous and intense phase of development that is performed according to legal and regulatory requirements of agencies such as the Food and Drug Administration (FDA) in the United States of America and the European Medicinal Evaluation Agency (EMEA) in Europe. Safe, effective and useful drugs that meet regulatory study requirements may receive a licence to be marketed and commercialised by the pharmaceutical company. In phase IV, additional efficacy and safety data are collected and can be used to identify new dosing schedules, discover how it compares with other available treatments, better understand its mechanism of action and find new applications. Drug development, although heavily regulated, rarely follows a linear process from phase I to phase IV, as there is a certain amount of overlap between phases in terms of data obtained.

II.III.I - Preclinical Studies

Initial toxicological screening of octreotide demonstrated a lethal dose 50% (LD_{50}) of 18 mg/kg in rats after acute administration [21]. Four-week studies in rats and dogs showed that octreotide was safe at a dose of 4-16 mg/kg/day and 0.2 mg/kg/day, respectively, following intraperitoneal administration. Pharmacokinetic data from the rhesus monkey showed an ID_{50} for GH secretion of 0.038 µg/kg/h octreotide, which was two orders of magnitude lower than the ID_{50} for insulin. For glucagon, the ID_{50} was approximately twice that for GH (0.075 µg/kg/h). The $t_{1/2}$ (elimination half-life) of subcutaneous octreotide was 40 min in rats and 74 min in dogs, and approximately one fifth of the dose was recovered unchanged in urine. From these rat data, octreotide inhibited GH 45 times more potently than somatostatin, and was 33 times more GH/insulin specific. This pharmacological profile was considered optimal, as it provided for much greater GH secretion and minimised the risk of hypoglycaemia through the higher ID_{50} for insulin suppression. Also, the elimination of octreotide was much slower than native somatostatin, thus increasing the likelihood of a long duration of action in humans.

Phase	Preclinical	IND	Phase I	Phase II	Phase III	NDA	Review	Phase IV
Duration (years)	6-7		1-2	2	3-4		1-2	Ongoing
Testing	Animals/cells		20-100 healthy humans	100-500 patients	1000-5000 patients			
Aim	Safety and activity assessment		Safety and dosage assessment	Safety and efficacy assessment	Long term safety and efficacy assessment		Review of results and regulators ruling	Refine and study further the safety and efficacy profile of approved drug

Figure 4. Diagram of timelines of various phases of drug development. IND = Investigational New Drug; NDA = New Drug Application. (For a useful overview of the important steps drug development process in the European Union, the European Medicines Evaluation Agency carries up to date information at http://pharmacos.eudra.org/F2/ pharmacos/docs/brochure/pharmaeu.pdf, while the Food & Drug Administration's Centre for Drug Evaluation Research maintains an informative website at www.fda.gov/cder/handbook/dev_rev.htm.)

Gastric acid secretion studies performed in rats showed that 0.5mg/kg octreotide had similar effects to cimetidine 10mg/kg[21]. Octreotide was also tested in rat tumour models and was shown to reduce oestrogen induced pituitary hyperplasia and insulinomas. After developing a specific radioimmunoassay (RIA) for octreotide, pharmacokinetic studies were performed in rats to evaluate its disposition as well as its distribution in different organs in rats. These studies showed the stability of octreotide in biological fluids and in tissues and that 50% of the octreotide dose was excreted in bile within 8 hours of subcutaneous administration[21]. Safety studies showed that octreotide was well tolerated in rats, dogs and monkeys. Overall, these characteristics made octreotide an attractive candidate for the treatment of diseases associated with hypersecretion of GH and gut hormones.

II.III.II - Phase I Clinical Studies

II.III.II.I - Clinical Pharmacology Studies

Based on these animal data, phase I pharmacological studies were performed in healthy human volunteers across a wide dose range via subcutaneous (sc) and intravenous (iv) routes of administration (*Table 1*). Single dose pharmacokinetic studies revealed that octreotide reached steady state after 90 min of iv infusion and the $t_{1/2}$ was 41-58 min. Peak octreotide concentrations occurred 15-30 min after single sc injections (50-100 µg). The $t_{1/2}$ was 113 minutes after sc injection, which was approximately 2.5 times longer than after iv administration. These human data confirmed and extended the animal results by showing rapid uptake of octreotide after sc injection, in conjunction with a prolonged elimination $t_{1/2}$. Studies in elderly volunteers (median age 76 years) revealed a longer half-life (140 min) and slightly increased area under the curve following single dose octreotide[22,23].

II.III.II.II - Pharmacodynamic Endocrine Studies

Pharmacodynamic and safety studies were performed to examine effects of octreotide on blood glucose concentrations and other aspects of glycaemic metabolism (results summarised and reviewed in [21, 22, 23]). Six healthy volunteers were treated with iv octreotide 50-100 µg/hr for 48 hours and glucose tolerance tests showed no changes in peak glucose concentration or area under the curve. The time taken to reach maximum glucose concentration was delayed[23]. In healthy volunteers post-prandial glucose con-

Participants	Route	Dose (µg)	$t_{1/2}\alpha$ (min)	$t_{1/2}\beta$ (min)	$t_{1/2}\gamma$ (min)	Vc (L)	Vd (L)	CL (ml/min)	AUC 0-∞ (µg/L • min)	AUC 0-480 (µg/L • min)	t_{max} (min)	Cmax (µg/L)
Healthy Volunteers	IV	25		9	72	5.2	18	177	153	153	3.7	5.7
	IV	50		11	90	5.9	21	159	338	342	4.1	9.6
	IV	100		11	99	6.2	30	227	648	670	3.4	24.2
	IV	200		14	98	10.2	29	198	1244	1271	7.3	27.8
Healthy Volunteers	IV	20						173				
Chronic renal failure	IV	20						75				
Healthy volunteers	SC	50	5.3		88		21.5		320	310	26	2.4
	SC	100	5.6		102		25.2		695	695	26	4.4
	SC	200	11.7		100		17.6		1734	1633	35	10.6
	SC	400	5.6		93		20		3163	3139	28	23.5
Healthy Volunteers	SC	50			113					298		1.9
	SC	100			113							2.7
Acromegalic patients	SC	100			110			172			27.4	3.4
	SC	100	24.1	11.3	169				896		42	4.5
	Nasal	500	11.3	12.9	148				957		16.5	8.7
		1000	7.9	17.3	155				1923		13.5	20.8
		2000	7.1	21.3	208				4597		13.8	43.4
Healthy Volunteers	Oral	2000								130	90-120	1.6
Healthy Volunteers (per-oral intubation studies)	Oral (S)	8000								72	60	0.77
	Oral (P)	8000								120	53	0.45
	Oral (L)	8000								112	45	1.06
	Oral (J)	8000								36	23	0.95
	Oral (I)	8000									12	0.52
Acromegalic patients	Oral	4000-8000									120-360	1.2

Table 1. Summary of the principal pharmacokinetic data after intravenous, subcutaneous, nasal or oral administration of octreotide. Abbreviations: AUC 0-∞ = area under the plasma concentration-time curve from time zero to infinity; AUC 0-480 = area under the plasma concentration curve from time zero to 480 minutes; CL = today body clearance (to convert to L/h, multiply by 0.06); Cmax = peak plasma concentration; $t_{1/2\alpha}$ = absorption half-life, $t_{1/2\beta}$ = distribution half-life; $t_{1/2\gamma}$ = elimination half-time; tmax = time to reach Cmax; Vd = volume of distribution; Vc = volume of central compartment; IV = intravenous; SC = subcutaneous; S = stomach; P = proximal duodenum, L = ligament of Treitz; J = jejunum; I = terminal ileum. Adapted from Chanson P, Timsit J, Harris AG[23].

centrations rose during treatment with octreotide at a dose of 150-1000 µg sc, although this was only significant (>200 mg/dL) at doses of 800 µg and 1000 µg[23]. Median post-prandial glucose levels were also found to be elevated in a dose dependent fashion following treatment with octreotide (100 - 600 µg twice daily)[23]. Overall, treatment of normal human subjects with octreotide was not associated with hypoglycaemia, even at high dose. GH secretion was inhibited by octreotide (50 µg once daily - 600 µg twice daily) in these healthy volunteer studies. Normal nocturnal and post-prandial GH surges were significantly suppressed by octreotide, while prolactin secretion at night was unaffected by octreotide. This implied that octreotide could provide good dynamic GH control in patient populations in response to the physiological stimuli encountered during sleep and nutrient metabolism.

II.III.II.III - Gastrointestinal and Pancreatic Function Studies

On a molar basis octreotide was 10 times more potent than native somatostatin in reducing gastric acid secretion[24,25]. Single sc injection of 100 µg octreotide inhibited gastric acid secretion for more than 5 hours[26]. With respect to pancreatic and biliary secretion, octreotide produced an 80% decrease in cholecystokinin (CCK) and secretin stimulated pancreatic secretion in healthy volunteers [27, 28, 29]. This inhibitory effect decreased with time. There was no decrease over time with respect to inhibition by octreotide of pancreatic enzyme secretion induced by Lundh meal[29]. Octreotide reduced amylase and trypsin output by three quarters[28]. Gallbladder contraction was also decreased in healthy volunteers, and the combination of this with pancreatic inhibition was suggested to raise the risk of reduced nutrient absorption. Lembke et al performed a double blind crossover study in nine healthy subjects over two seven day periods[29]. Faecal fat excretion was higher during octreotide treatment but this effect decreased with time. Other individual studies demonstrated that octreotide reduced caerulin-stimulated pancreatic polypeptide release, but had no effect on basal secretion of this gut hormone [30, 31, 32]. Creutzfeldt et al found that low dose octreotide (25 µg) was able to reduce meal-stimulated pancreatic polypeptide completely, while lesser effects were seen on insulin and glucagon secretion[33].

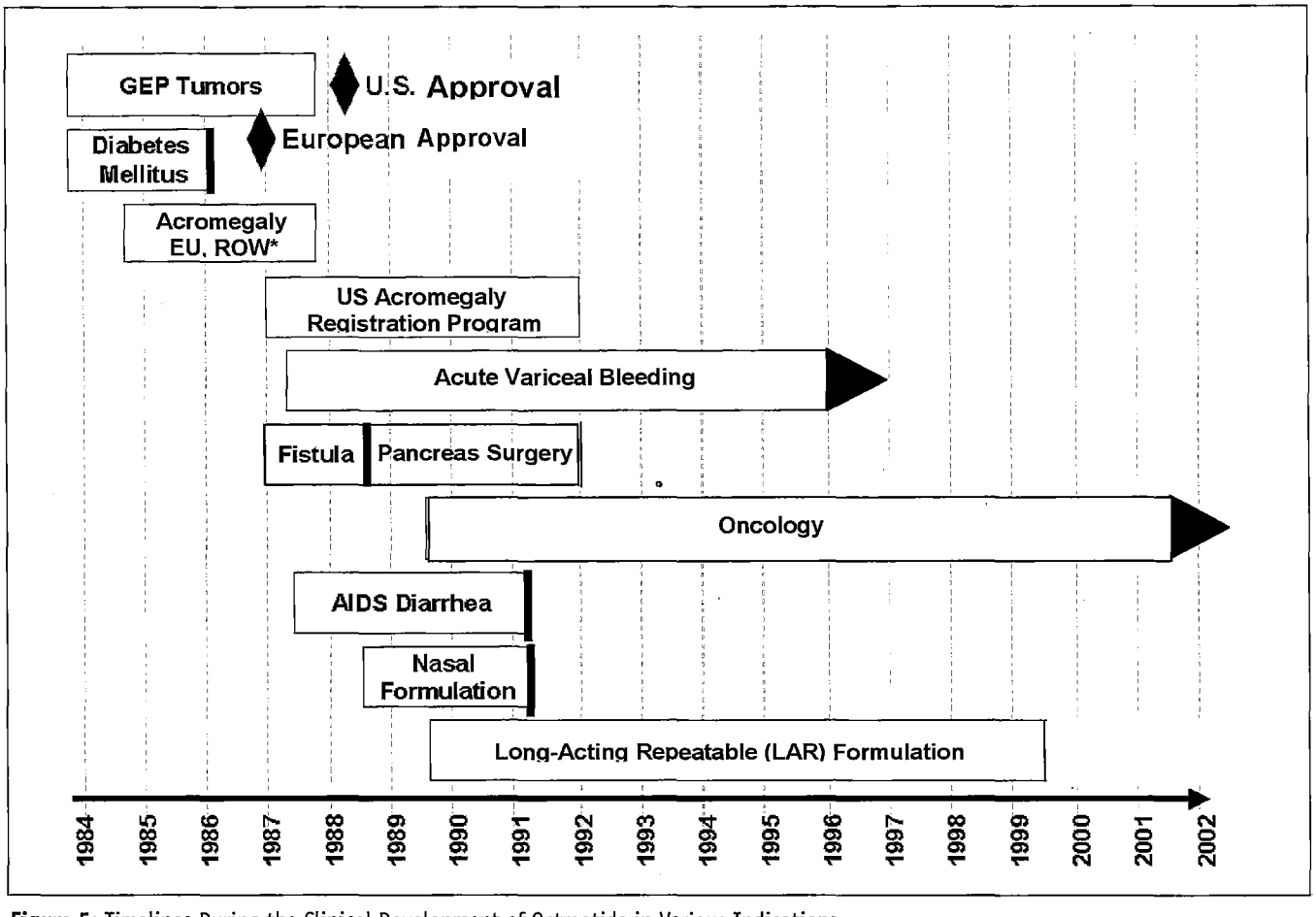

Figure 5: Timelines During the Clinical Development of Octreotide in Various Indications

* *EU: European Union (previously European Community)*
ROW: Rest of the World

II.III.II.IV - Gastrointestinal Motility Studies

CCK-induced gallbladder contraction was inhibited by octreotide but this effect disappeared after treatment for six days[29]. This may have been due to desensitisation of the gallbladder. However, gallbladder contraction in response to a Lundh meal remained suppressed completely by 25 µg octreotide after six days of treatment. Octreotide increased gastric motility but inhibited intestinal motility (increased transit time)[34]. Also, octreotide reduced intestinal mucosal blood flow to a greater degree than native somatostatin[25,26,35].

II.III.II.V - Safety Studies

With regard to safety parameters, octreotide had no clinically significant effects on liver enzymes, triglycerides, renal and haematological profiles, electrocardiograms or vital signs[22,23]. Patients reported abdominal discomfort, nausea, loose stools and diarrhoea among the most common adverse events associated with octreotide. These were accompanied by a rise in stool fat, presumably due to reduced exocrine pancreatic secretion. Flushing also occurred, and along with abdominal symptoms appeared to be dose related in that most patients at the highest dose (1000 µg) reported symptoms. These adverse events were self-limiting, however, and no serious sequalae occurred during this phase of development.

II.III.III - Impact of Phase I Studies

At the outset our primary indication for octreotide was as a treatment for diabetes mellitus and its complications. The results from phase I studies demonstrated multiple inhibitory effects on hormones (particularly GH with respect to diabetes mellitus) and gastrointestinal motility, which suggested multiple potential clinical uses. Initially, however, our focus remained firmly on using the preclinical and phase I studies to demonstrate safety and efficacy in terms of diabetes mellitus treatment. The disparate nature of the potential applications of octreotide provided an excellent opportunity for our assessment of the Clinical Development Program when the diabetes mellitus indication was proving unsuccessful. Studies with native somatostatin had suggested octreotide as a possible treatment in gut endocrine tumours[36] and acromegaly[37], which led to the distribution of octreotide on a compassionate use basis in these two indications.

A unique aspect of octreotide's clinical development was that multiple putative indications were eventually pursued in parallel *(Figure 5)*. The prevailing model at the time - and currently - was to develop potential drugs for one tightly defined indication, in this case, diabetes mellitus. After completion of the preclinical phase and phase I, the pharmacological characteristics of octreotide i.v. and s.c. were all published in peer reviewed literature e.g. [38,39]. During this period, alternative delivery forms of octreotide were in development, including a nasal insufflation powder[40,41] and an oral formulation[42,43,44].

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Chapter III.

The Clinical Development of Octreotide in Diabetes Mellitus

III.I - CHARACTERISTICS OF DIABETES MELLITUS

III.I.I - Glycaemic Control in Diabetes Mellitus and the GH/IGF-1 Axis

The Clinical Development Program for octreotide in type I diabetes mellitus was based on the existing understanding of the role of growth hormone (GH) and insulin-like growth factor-I (IGF-1) in the regulation of carbohydrate metabolism (hormonal and gastrointestinal), and in the aetiology of diabetic retinopathy and nephropathy. It had long been recognised that patients with poorly controlled type I diabetes mellitus exhibited elevated GH levels[1]. It was felt that this GH hypersecretion in conjunction with increased circulating glucagon levels contributed to poor glycaemic control and long-term complications[2,3]. It had been demonstrated that GH administration could elevate plasma glucose, while conversely, improved glycaemic control reduced GH levels in type I diabetic patients[4]. It has since been shown that reduced GH secretion enhances insulin sensitivity in type I diabetic patients[5]. The so-called "dawn phenomenon", an early morning (~ 4 am) rise in blood glucose is temporally associated with a parallel surge in GH, a phenomenon which was felt to represent an important target for improved diabetic control. When we formulated the Clinical Development Program for octreotide in diabetes mellitus, octreotide therapy was seen as a method for reducing the hyperglycaemic effects of GH, especially during nocturnal surges. Consequently, it was suggested that octreotide administration in type I diabetes mellitus could reduce insulin requirements.

The aetiology and clinico-pathological findings in type II diabetes mellitus differ significantly from autoimmune type I disease. Insulin resistance is the primary characteristic of type II diabetes mellitus. It is currently held that metabolic dysregulation decreases the sensitivity of liver, muscle and other cells to insulin[6], which causes elevated blood glucose and hyperinsulinaemia. This metabolic syndrome can be accompanied by elevated low-density lipoprotein (LDL) cholesterol and triglycerides and hypertension, which combine to cause increased morbidity and mortality (especially vascular) in type II diabetes mellitus. Obesity and genetic traits can worsen insulin resistance, as can hormones such as GH. Patients with acromegaly are now recognised to have significant insulin resistance[7], with 30-40% developing impaired glucose tolerance and 10-20% developing overt diabetes mellitus. In the early to mid 1980's research had demonstrated that GH affected both hepatic and peripheral insulin sensitivity in normal and acromegalic individuals[8,9], while insulin secretion itself was possibly unimpaired[10]. Subsequent studies in the 1990's using recombinant GH in patients with short-stature or hypopituitarism have confirmed that GH decreases insulin sensitivity significantly[11,12]. At the inception of the Clinical Development Program for octreotide we were aware of some of these interactions between GH and glucose metabolism in type II diabetes. We also noted that blood glucose could potentially be lowered via inhibition by octreotide of gastric hormones and motility. We hypothesised that by slowing gastric motility, the entry of carbohydrate rich material into the duodenum could be slowed, thus reducing uptake of mono- and disaccharides into portal blood. The Clinical Development Program in type II diabetes mellitus focused primarily on the metabolic effects of octreotide on glycaemic control.

III.I.II - Complications of Diabetes Mellitus

At the time of the clinical development of octreotide for diabetes mellitus in the 1980s, it was recognised that morbidity and mortality was due largely to macro- and micro-angiopathic changes. With respect to microangiopathic diabetic complications, GH and IGF-1 had been implicated in neovascularisation in diabetic retinopathy and renal hypertrophy in diabetic nephropathy[13,14,15]. The precise mechanisms by which these pathological effects occurred was unclear, but our working hypothesis at the time was that

octreotide could retard retinal revascularisation and early kidney hypertrophy in type I diabetes mellitus via GH suppression. In the mid 1980's the concept that diabetic glycaemic control was a key determinant of disease outcome in type I diabetes mellitus was unproven. Prospective evidence only became available in the 1990's when the Diabetes Control and Complications Trial (DCCT) showed that intensive glycaemic control reduced the risk of retinopathy and albuminuria by 47% and 54%, respectively[16]. Our aims for octreotide in type I diabetes mellitus were pragmatic, namely to improve glucose control and (consequently or independently) reduce microvascular retinal and renal complications.

III.II - THE ROLE OF THE GH/IGF-1 AXIS IN DIABETES MELLITUS

III.II.I - GH/IGF-1 and Insulin Regulation

The mechanisms by which GH affects insulin sensitivity, and hence the severity of diabetes, are still not fully understood. Animal studies have suggested that GH reduces hepatic insulin receptor numbers [17,18], causing increased circulating plasma insulin. Glucose transport proteins such as GLUT1 are decreased in response to GH [19], and are increased in GH deficiency[20]. Therefore, GH-induced insulin resistance may be due to reduced uptake from serum into storage tissues such as hepatocytes and adipocytes.

As virtually all of the known growth-promoting activities of GH are mediated at a tissue level by IGF-1, much research has focused on its role in diabetes mellitus. IGF-1 and two of its binding proteins (IGFBP's), IGFBP-1 and IGFBP-3, are known to influence carbohydrate metabolism. IGFBP-3 functions as a high affinity carrier protein for IGF-1 and generally has a stable concentration throughout the day, whereas IGFBP-1 is more sensitive to metabolic changes[21]. In type I diabetes mellitus, the IGF-1/IGFBP system is abnormal; GH secretion is increased[22] but circulating IGF-1 is low [23]. This apparent paradox is currently thought to be due to initial hyperglycaemia-induced down-regulation of hepatic IGF-1 production and consequently, serum IGF-1. Later, these low levels of IGF-1 feed back to the pituitary and stimulate GH production. Therefore, this hormonal disturbance is caused by a disconnect between the central and peripheral arms of the GH-IGF-1 axis[24,25]. Patients with type II diabetes mellitus have more heterogeneous disturbances of GH/IGF-1/IGFBP. Low insulin levels in type I diabetes mellitus are known to decrease hepatic GH receptors[26,27], and thus decrease the synthesis and release of IGF-1 in response to GH. Furthermore, hepatic IGFBP-1 production is inhibited by insulin[28,29] and insulinopaenia increases IGFBP-1.

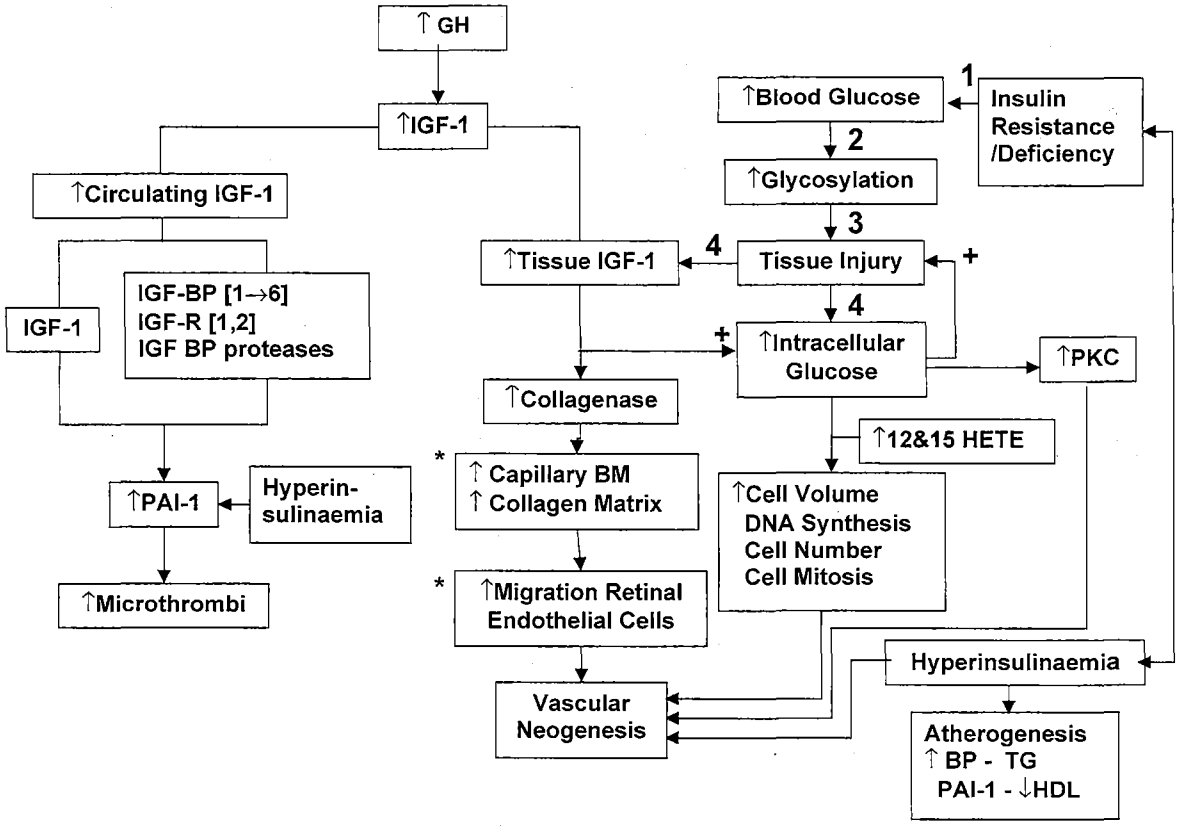

Figure 6. Roles played by insulin-like growth factor-1 (IGF-1), IGF binding proteins (IGF-BP), IGF-receptors (IGF-R) in the development of complications related to diabetes mellitus. BM = basement membrane, PKC = Protein kinase C; PAI-1 = Plasminogen activator inhibitor-1; BP = Blood pressure; TG = Triglycerides; HDL = High density lipoprotein, HETE = hydroxyeicosatetraenoic acid. 1, 2, 3, 4 = sequence of events. Drawn from Merimee[32].

III.II.II - GH/IGF-1 and Complications of Diabetes Mellitus

In a recent review of the role of growth factors in the pathogenesis of diabetic vascular complications, Blakesley and colleagues conclude that one or more growth factors, such as, IGF-1, fibroblast growth factor (FGF), epithelial growth factor (EGF), vascular endothelial growth factor (VEGF) or transforming growth factor beta (TGF-beta), play a significant role in the initiation and progression of the pathologic changes seen in diabetic retinopathy and nephropathy [30]. Elevated serum (and possibly vitreous) IGF-1 levels have been associated with proliferative retinopathy and retinal neovascularisation; and rodent studies indicate that IGF-1 and/or GH can lead to mesangial cell proliferation, glomerular sclerosis, and glomerular hyperfiltration. Janssen et al, however, have questioned the pathogenic role of the IGF/IGFBP system in the development of diabetic complications at the tissue level, as their studies failed to correlate serum levels of IGF-1 and IGFBP with their respective tissue levels [31]. In a comment on these findings Merimee reviewed the evidence in support of IGF-1 and IGFBP in the pathogenesis of diabetic microvascular complications and noted a number of potential interfaces between IGF-1 and vascular complications, most particularly diabetic retinopathy [32]. Figure 6 summarises the various strands of evidence regarding the role of IGF-1 in diabetic complications.

III.II.II.I - Diabetic Retinopathy

Diabetic retinopathy is a leading cause of adult blindness [33] and after 10-15 years of diabetes there is a 90% chance of developing retinopathy [34]. It is estimated that in the United States, 12,000 to 14,000 diabetic patients lose their sight from retinopathy each year [33]. Diabetic retinopathy results from extensive proliferation of new retinal blood vessels and visual acuity is lost due to vitreous haemorrhage or fluid loss from fragile new vessels. Panretinal argon laser photocoagulation is the only effective intervention for proliferative diabetic retinopathy but it can have complications such as retinal detachment; it is a destructive procedure and does not always provide control of proliferative retinopathy. *Figure* 7 summarises in a schematic fashion some of the important pathological steps in terms of retinal vascular changes and highlights some important growth factors that are currently understood to play an important role in mediating pathological changes in the retinas of diabetic patients.

At the time of the development of octreotide, there was historical evidence for the role of GH in diabetic retinopathy. Pituitary ablation retards the progression of diabetic retinopathy [35] and clinical trials have demonstrated the efficacy of elective hypophysectomy (surgical or Yttrium-90 radioactive beads) in preventing blindness [36,37]. The severity of hypopituitarism [38] and GH deficiency [39] and the duration following pituitary ablation correlate with the degree of neovascularisation [40,41]. Retinal capillary hyperfragility in diabetes mellitus also improves after pituitary ablation [42]. Merimee's original report that diabetic GH-deficient patients exhibited a lower rate of retinopathy than other diabetic patients [43] has been confirmed by others [44]. Preclinical studies have shown a direct stimulatory effect for GH on the retinal vascular endothelium [45]. A more recent report has shown that exogenous GH treatment in GH-deficient, non-diabetic patients can cause retinopathic changes similar to those seen in diabetes mellitus [46].

Little was known about the role of IGF-1 in diabetic retinopathy when the Clinical Development Program for octreotide in diabetes was designed. In 1983, Merimee and colleagues found that total IGF-1 was elevated in patients with early neovascular retinal changes [13]. In contrast, Flyvbjerg and Orskov reported subsequently that circulating IGF-1 was normal in type I diabetic patients compared to a matched non-diabetic control population [47]. Grant and others have noted that diabetic patients with proliferative retinopathy have three times the vitreous IGF-1 concentrations of age-matched non-diabetic controls, while IGFBP's also rise [48,49]. In a porcine model, retinal microangiopathy was induced by direct injection of IGF-1 into the vitreous [50]. In recent years, the interplay between IGF-1 and its binding proteins has become better understood. Janssen et al reported that fasting free IGF-1, total IGF-1 and IGFBP-3 were lower in type

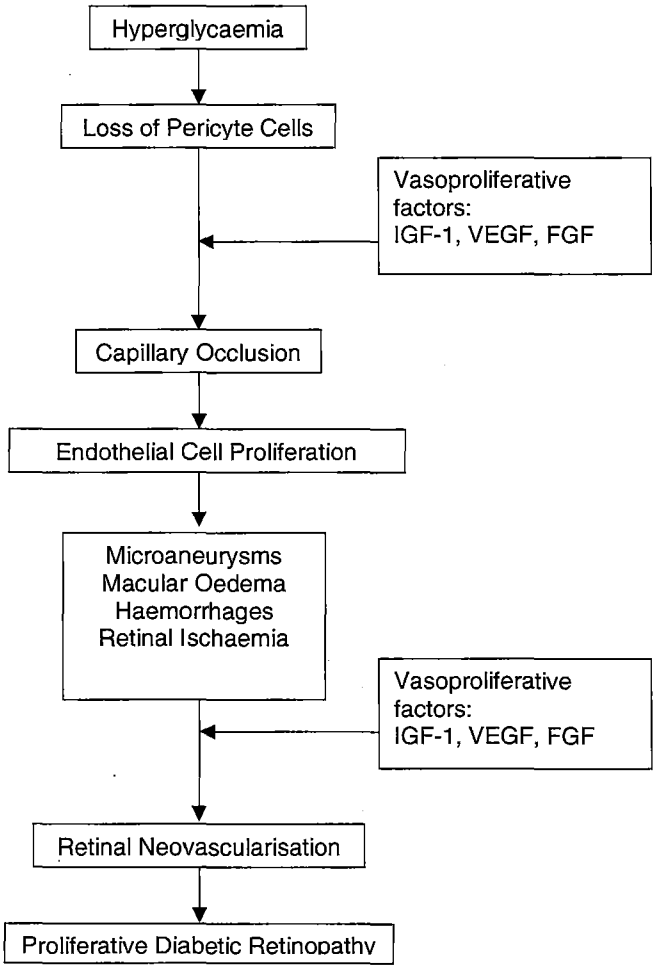

Figure 7. Diagrammatic representation of the pathogenesis of diabetic retinopathy.

I diabetic patients, while IGFBP-1 was higher[31]. Interestingly, free IGF-1 (age-adjusted) was higher in type I diabetic patients with retinopathy than diabetic patients without retinopathy, although the authors cautioned that the opthalmoscopic assessment of retinopathy was subjective and could have resulted in mis-classification of some patients. Further evidence of the role of IGF-1 in diabetic retinopathy has come from studies of human recombinant IGF-1. The finding that IGF-1 is reduced in diabetes and that exogenous IGF-1 can improve hyperglycaemia led to a clinical trial, which demonstrated a progression of diabetic retinopathy in IGF-1-treated diabetic patients[51,52].

III.II.II.II - Diabetic Nephropathy

Approximately 25-50% of diabetic patients develop nephropathy and a significant proportion will require costly dialysis or renal transplantation. Diabetic nephropathy is now the commonest cause of renal failure in developed countries[53], and the cost of diabetic nephropathy was $2 billion in the Unites States in the early 1990's[54]. From 1981 to 1990, the number of diabetic patients requiring dialysis or transplant for end-stage renal failure rose by 10% year-on-year[55]. Furthermore, diabetic patients with nephropathy have 25 - 40 times the all-cause mortality of age-matched non-nephropathic patients. The morphological changes of early diabetic nephropathy have been well characterised. They include increased glomerular volume, increased glomerular capillary lumen area, and expansion of the mesangial cell volume[56,57]. The first measurable manifestation of this is increased glomerular filtration rate. Although the progression of diabetic nephropathy is slow, 30 - 40 % of patients with type I diabetes may progress to renal failure.

In experimental diabetes mellitus in rats, renal mesangial cells develop elevated numbers of IGF-1 receptors and kidney IGF-1 levels rise within the first four days, peaking at 24 to 48 hours after induction of the diabetes[58,59]. In the absence of GH, however, renal hypertrophy is abolished in experimental diabetes in rats[60]. The primary role of IGF-1 in diabetic nephropathy appears to be glomerular and mesangial cell expansion, as IGF-1 can induces protein synthesis by mesangial cells in culture[61]. Mesangial cell expansion contributes to the overall kidney growth and mesangial cell protein synthesis may contribute to the basement membrane thickening that is characteristic of glomerulosclerosis[62,63]. IGF-1 has a less clear role in causing increased GFR during the development of diabetic nephropathy. Because there is a lack of correlation between declining GFR and increasing kidney size in patients with diabetic nephropathy and because circulating IGF-1 levels do not strictly correlate with renal hypertrophy, other factors are likely to be contributing to declining renal function. However, it is known that GH administration can normalize the low renal plasma flow (RPF) and low GFR seen in GH-deficient patients; and serum levels of IGF-1 are seen to increase concomitantly[64,65]. In type I diabetic patients, GH hypersecretion has been correlated with glomerular hyperfiltration[66] and exogenous GH administration in poorly controlled diabetic patients increases glomerular filtration[67]. Since transgenic mice expressing increased GH develop glomerulosclerosis but mice transgenic for IGF-1 hypersecretion do not, it may be that both GH and IGF-1 play a combined role at different stages of diabetic nephropathy.

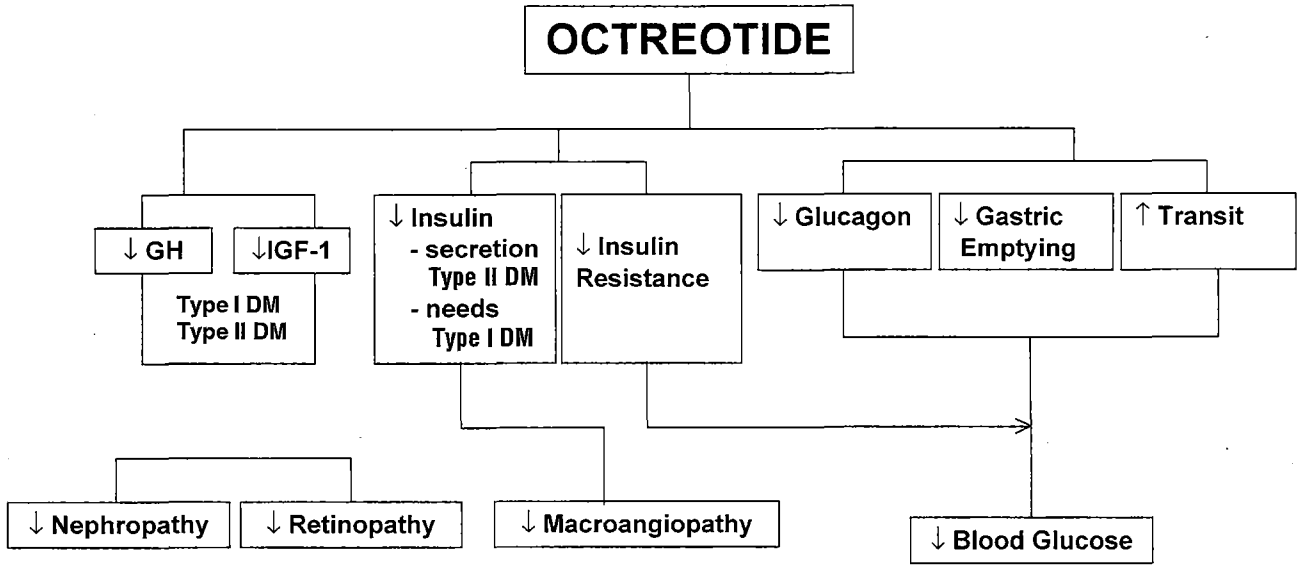

Figure 8. Proposed mechanisms by which octreotide could influence blood glucose concentration and complications in patients with Type I and Type II diabetes mellitus (DM).

Circulating and locally generated IGF-1 appear to be involved in the development of diabetic nephropathy. The IGF-1 synthesised locally in the kidney is regulated in part by GH [68,69,70]. IGF-1 receptors are found throughout the kidney [71,72,73], including in mesangial cells. There is a likely synergism between IGF-1 and other growth factors such as epithelial growth factor (EGF) and transforming growth factor-β (TGFβ) [74,75,76]. IGF-1 and IGFBP's may interact with vasoactive factors and kinins to link diabetic nephropathy with hypertension. IGF-1 infusion in rats decreases glomerular afferent and efferent arteriolar resistance and this vasodilatory effect may be mediated by kinins, which also have the effect of increasing renal plasma flow [77,78]. Kinins appear to cause vasodilation via nitric oxide and interestingly, inhibition of nitric oxide synthesis blocks the vasodilator effect of IGF-1 [79]. IGFBPs may also play a role in modulation of IGF-1 related tissue growth in various parts of the kidney, as increased renal cortical and medullary IGFBP and IGF-1 receptor numbers have been noted in animal studies [80,59].

III.III - OTHER CELLULAR PATHOLOGICAL MECHANISMS IN DIABETES MELLITUS

Hyperglycaemia in diabetes mellitus favours biochemical disturbances that can be detrimental to tissue. Glucose itself can be toxic to cells, while glycosylation, hypoxia and free radical generation can damage proteins, alter membrane function and induce inflammatory cell repair mechanisms. Glycation of lysine terminal groups in protein leads to cross-linking between or within proteins resulting in compounds called advanced glycosylation end products (AGEs). AGEs may alter cell-cell interactions between immune cells like macrophages and vascular endothelial cells, producing cytokines and IGF-1 [81]. They may also induce collagen cross-linking and basement membrane thickening and mesangial cell matrix production [82]. Cutaneous AGEs in diabetic patients have been shown to increase progressively with the severity of retinopathy [83]. Aldose reductase (AR) and sorbitol dehydrogenase act with NADH to maintain osmotic balance across cell membranes. AR is expressed in retinal capillary pericytes, retinal pigment epithelium and retinal endothelium. AR expression and sorbitol concentrations have been found to be elevated in association with retinal dysfunction and hyperglycaemia. AR inhibitors can prevent the progression of diabetic retinopathy, including reduction or disappearance of microaneurysms, haemorrhage, and cotton wool spots [84]. Increased intracellular glucose can initiate biochemical reactions resulting in neovascularisation [85], possibly via increased protein kinase C [86]. Mesangial cells exposed to elevated glucose concentrations synthesize less heparan sulfate, which could alter transcapilliary charge and promote proteinuria [54]. Intracellular hyperglycaemia and auto-oxidation results in the production of oxygen free radicals that cause protein damage. Oxidative products of glycated proteins are found in elevated concentrations in patients with diabetic retinopathy, indicating an increase in oxidative protein damage by glycooxidation. There is some evidence of decreased natural antioxidant system activity in experimental and human diabetes [87]. Temporary occlusion of the retinal circulation in rats leads to a proliferative response in both retinal capillary endothelial cells and pericytes [88]. IGF-1 is released from cultured retinal microvascular endothelial cells, pericytes and pigment epithelial cells in response to hypoxia. Also the production of IGFBP's is increased as oxygen tension decreases [89].

While it has been suggested that chronic hyperglycaemia is directly toxic to cells, damage at a tissue level in diabetes mellitus is more likely to be caused by the actions of disparate growth factors, cytokines and biochemical pathways. Evidence has been put forward for a crucial role for many cellular messengers and mechanisms in the development of retinopathy and angiopathy in diabetes mellitus (*see Figures 6 and 7 above*).

III.IV - THE CLINICAL DEVELOPMENT PROGRAM IN DIABETES MELLITUS

III.IV.I - Scientific Rationale

As noted previously, somatostatin inhibits GH, IGF-1 and gut hormones such as insulin, glucagon, gastrin, cholecystokinin, vasoactive intestinal peptide and motilin. In the gut somatostatin's effects are manifested as decreased gastrointestinal blood flow and motility; decreased gastric acid secretion, decreased carbohydrate absorption and increased water and electrolyte absorption. In both type I and type II diabetes mellitus, basal somatostatin release is increased while the somatostatin response to food is impaired. Normalisation of glycaemic control using an artificial pancreas (Biostator) has the effect of also normalising somatostatin levels [90,91,92]. Besides the impairment of insulin secretion and insulin sensitivity in diabetes mellitus, glucagon and somatostatin release are also abnormal and contribute to the development of hyperglycaemia. The diabetogenic effect of glucagon is mediated mainly by increased glycogenolysis and gluconeogenesis. In the case of somatostatin, the impaired response to food will contribute to the postprandial glycaemic rise due to enhanced transit of nutrients in the gut. Short-term studies with iv somatostatin in type I and insulin-treated type II diabetic patients improved glycaemic control and had an insulin sparing effect [93]. With respect to octreotide, we felt that glycaemic control could be improved by suppressing GH and glucagon secretion and slowing gastric motility and carbohydrate absorption (*Figure 8*). When designing the Clinical Development Program we were acutely cautious regarding the potential for octreotide to adversely affect diabetes mellitus via acute hypoglycaemia or worsening hyperglycaemia. In order to address this difficulty, we designed and executed a comprehensive program of safety studies in both healthy volunteers and in patients with type I and type II diabetes.

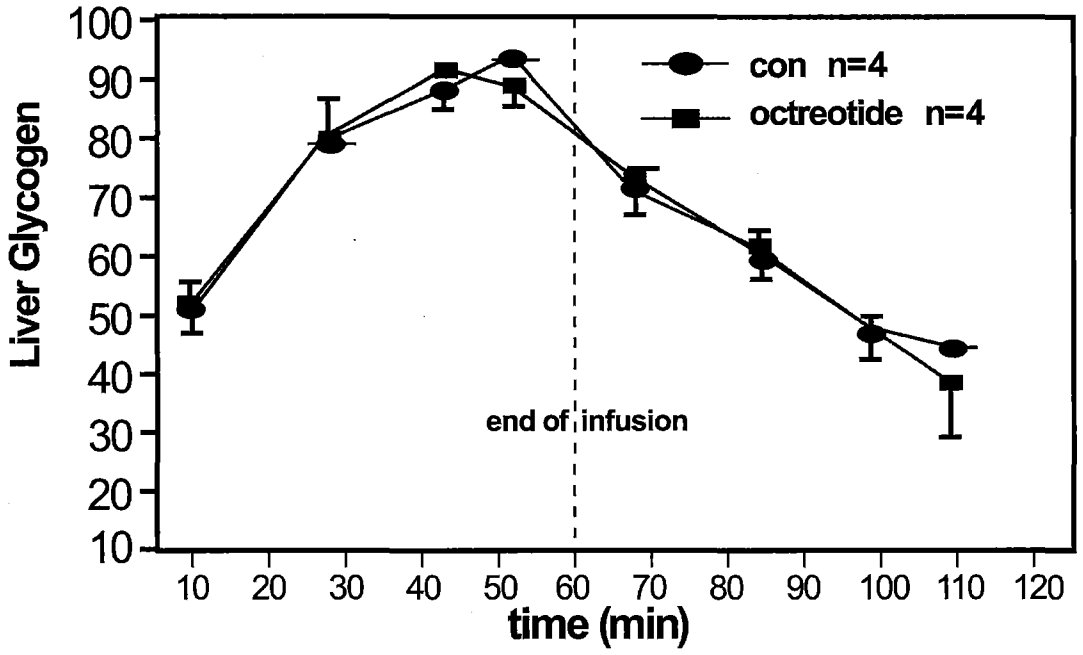

Figure 9. Effect of octreotide (10 µg/kg/min) or saline on in vivo rat liver glucose in fasted rats.[13] C-labelled glucose was infused with octreotide or saline (con) for 60 min and continued alone for the subsequent 60 min. Each time course represents the mean ± SD of [13]C NMR signal intensities derived from four separate experiments with four animals in each treatment group. Maximum signal intensity for liver glycogen was arbitrarily set at 100. The figure demonstrates that octreotide treatment had no impact on glucose handling when compared with placebo in this model. Adapted from Ezzat S, Pahl-Wostl C, Rudin M, Harris AG[94].

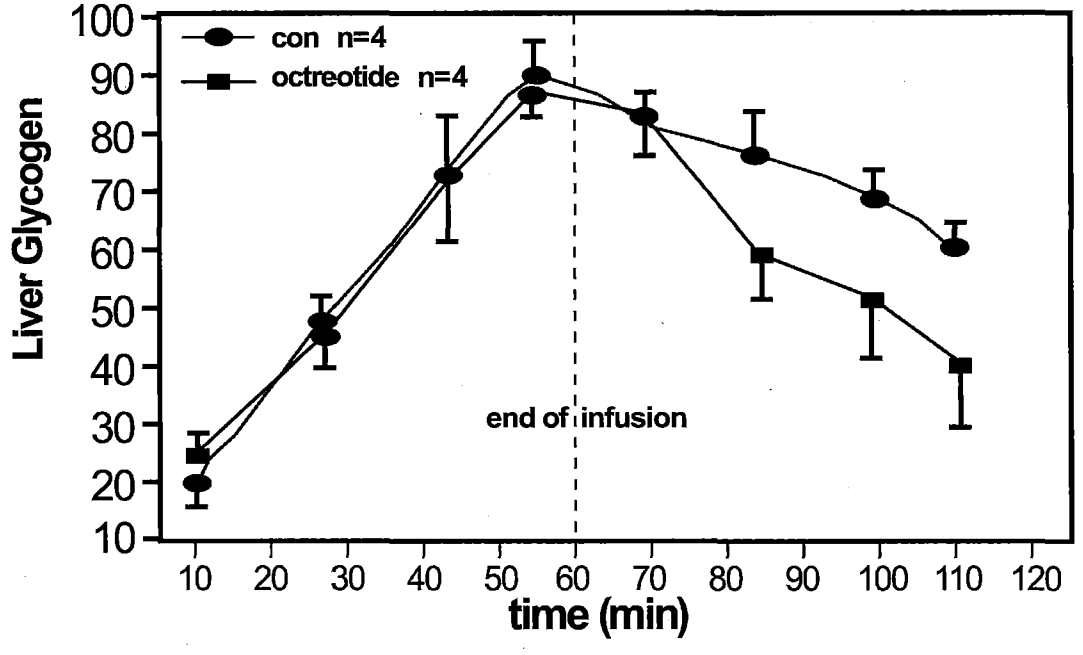

Figure 10. Effect of octreotide (10 µg/kg/min) or saline on in vivo rat liver glycogen in fasted rats.[13] C-labelled glucose was infused with octreotide or saline (con) for 60 min and continued alone for the subsequent 60 min. Each time course represents the mean ± SD of [13]C NMR signal intensities derived from four separate experiments with four animals in each treatment group. Maximum signal intensity for liver glycogen was arbitrarily set at 100. The figure demonstrates that octreotide treatment was associated with greater glycogen breakdown than placebo treatment. Adapted from Ezzat S, Pahl-Wostl C, Rudin M, Harris AG[94].

III.IV.II - Octreotide: Effect on Metabolic Control in Diabetes Mellitus

III.IV.II.I - Background Studies

In order to characterise the effect of octreotide on metabolic control and complications in diabetes mellitus, a group of 29 individual studies were performed, involving 141 type I and 61 type II diabetes patients. Particular attention was paid to potential adverse events, especially hypoglycaemia, as the effect of octreotide on glucose suppression in diabetes had not been fully investigated at that time. The extensive study program involved many trials performed by numerous groups worldwide. Studies wich have been previously reported only in abstract form were summarised with S. Efendic and M. Gutniak (see footnote below).
Type I diabetes patients were insulin deficient (C peptide negative) with HbA1C < 11% and free of major diabetic complications with particular reference to autonomic neuropathy. Type II diabetes patients were non-insulin treated with fasting or postprandial hyperinsulinaemia (C peptide > 200 pmol/ml) and below 130% ideal body weight. Fasting blood glucose levels were > 180 mg/dl and post prandial blood glucose levels were > 60 mg/ml and < 200 mg/dl. Also, gastrointestinal side effects of octreotide were studied actively, and in some trials faecal fat excretion was measured to better characterise the effect of octreotide on dietary fat absorption in diabetes. The efficacy parameters chosen were blood glucose (peak, time to peak, AUC), insulin requirement in type I diabetic patients, C-peptide levels in type II diabetic patients, and hormonal profiles (GH, glucagon, cortisol, adrenaline/noradrenaline). Together with Ezzat and colleagues, we used nuclear magnetic resonance spectroscopy to study the effect of octreotide on the fate of 13C-labeled glucose administered to fasted and well-fed rats[94]. We found that octreotide did not interfere with glycogen synthesis but significantly accelerated the onset of glycogenolysis (*Figure 9, 10*). Studies in conscious dogs have shown that the suppressant effect of octreotide on plasma glucose after an oral glucose tolerance test is mainly due to inhibition of glucose absorption as well as the suppression of hepatic glucose output[95].

III.IV.II.II - Healthy Volunteer Studies

A placebo-controlled double-blind study in healthy volunteers showed that 50 µg bolus and 50 µg octreotide per hour for four hours did not significantly impair glucose counter-regulatory hormone responses to experimental insulin-induced hypoglycaemia. Following on from this, it was demonstrated that octreotide (50 µg s.c.) delayed meal induced hyperglycaemia when administered 30 minutes before eating. Multiple dose studies using 25 µg octreotide twice daily before meals for one week reduced gastrointestinal absorption and pancreatic hormonal function. These results demonstrated safety and efficacy for octreotide, and particularly highlighted no counter-regulatory hormone inhibition and no hypoglycaemia with octreotide[96]. In a study of nine healthy volunteers, Kahn and colleagues noted that octreotide (50 µg bid) suppressed fasting and glucose-stimulated insulin secretion, leading to mild fasting hyperglycaemia[97]. They concluded that these changes in insulin secretion were due to lower pancreatic B-cell sensitivity to glucose, rather than diminished B-cell secretory capacity. Also the effect of octreotide to decrease B-cell sensitivity did not lead to insulin resistance, rather, octreotide was associated with relative glucose resistance as assessed by reduced B-cell glucose responses at basal and zero levels of insulin.

Subsequently Vogt and Petrides studied six healthy volunteers to examine the effects of chronic changes in plasma insulin concentration on insulin sensitivity[98]. Glucose turnover and other glucose parameters were measured before and after administration of octreotide (200 µg/day for 4 days sc infusion). This treatment decreased post-absorptive and meal-stimulated plasma insulin levels by approximately 30-40%, but did not significantly alter overall glucose tolerance, free fatty acid, growth hormone, or glucagon levels. Furthermore, octreotide was associated with significantly increased insulin-mediated whole body glucose disposal, non-oxidative glucose disposal, and fractional glycogen synthase activity. Placebo did not alter metabolic parameters. The authors concluded that lowering plasma insulin concentration over a prolonged period increases insulin sensitivity.

III.IV.II.III - Metabolic Effects of Octreotide in Type I Diabetes Mellitus

We performed studies in Type I diabetic patients, beginning with glucose and gut hormone profiles. Octreotide was no different from placebo in terms of glucose dynamics during insulin-induced hypoglycaemia and subsequent recovery. This occurred despite significant reduction in GH and glucagon secretion, however counter-regulation via cortisol, epinephrine and pancreatic polypeptide were unaffected. The overwhelming majority of studies were randomized double blind placebo controlled and cross over design. Patients were well versed with the control of their own diabetes and adjusted their insulin dosage accordingly in order to prevent hypoglycaemia possibly due to improved tissue sensitivity of insulin. Patients continued their normal diet, exercise and insulin regimen throughout the study. The criteria for efficacy were based on reduction of insulin dose and/or improvement in blood glucose control. As insulin doses were freely modified according to the patient's needs, this was considered to be a confounding factor in terms of linking possible improved blood glucose control exclusively to the addition of octreotide. To this end, insulin doses and the number of study days during which blood glucose control was improved during octreotide as compared to placebo were taken into consideration.

A number of these studies were published in abstract form, which can be found summarized in : Harris AG, Gutniak M, Efendic S. Somatostatin analogue therapy of diabetes mellitus. In: New antidiabetic drugs. (ed.) CJ Baily, PR Flatt. Smith Gordon, Nishimura 1990: 279-288.

Overnight Metabolic Profile Studies: Effect of Bedtime Octreotide in Type I Diabetes Mellitus

In a euglycemic clamp study seven patients with Type I diabetes received 50 µg octreotide sc or placebo at 11pm after having been stabilized with a constant intravenous glucose infusion. During the next 24 hours, glucose levels were kept constant so that the effect of octreotide was assessed by the patients' insulin requirements. No insulin was required between 11pm and 1am in the octreotide treated patients. However insulin requirements were not altered by octreotide between 3am and 9am. Mean GH and peak GH levels were significantly reduced between midnight and 2am compared to placebo. In another euglycaemic clamp study five patients with type I diabetes received 50 µg octreotide or placebo at 11pm. Insulin requirements were significantly reduced at dawn between 3.30am and 7.30am. GH levels were significantly reduced between 11.30pm and 3am. Glucagon and cortisol levels remained unaffected.

In puberty, a temporary rise in insulin resistance occurs. As other putative causes of pubescent insulin resistance, such as, a rise in body mass index, increased fat deposition, and sex hormone secretion have been shown not to cause insulin resistance in puberty, it is likely that GH and IGF-I increases are of central importance[99,100,101,102], particularly at night due to nocturnal GH spurts. Thus, together with Aarsen and Bruining et al we studied overnight hormonal profiles and the effects of octreotide in 10 type I diabetic patients aged 12-16 years old[103]. Patients were studied on two different nights one week apart and were randomised to receive either a single dose of 50 µg of octreotide sc or placebo at 10pm in a double blind, cross-over design. No changes were made to insulin therapy or diet during the study period. Bedtime octreotide was associated with suppression of GH levels over the following 4 hours, and blood glucose concentrations fell concomitantly. Early morning glucose rises were not inhibited by octreotide administration, and glucagon levels were suppressed only at one time point 120 minutes after octreotide administration. Interestingly, however, 3-hydroxybutyrate levels were lower following octreotide therapy compared with placebo (*Figure 11, 12*). From the results of this study we concluded that it was likely that the duration of action of octreotide was too short to have a marked impact on the early morning rise glucose concentration. The fact that triglyceride and free fatty acid mobilisation and gluconeogenesis were not impacted by octreotide compared with placebo leads to the possibility that hepatic ketogenesis was reduced by octreotide. As glucagon was unaffected by octreotide administration in this study, it may be that hepatic ketogenesis was altered indirectly by octreotide via a suppressive effect on GH or IGF-I. There was no difference in the diabetogenic effect (gluconeogenesis) of GH surges at night between patients receiving a continuous insulin infusion compared with those on intermittent injected insulin. It appears, therefore, that the diabetic state is the determinant of the diabetogenic effect of GH, rather than variations in insulin concentration at night. We noted that the reduction in both ketogenesis and blood glucose following octreotide

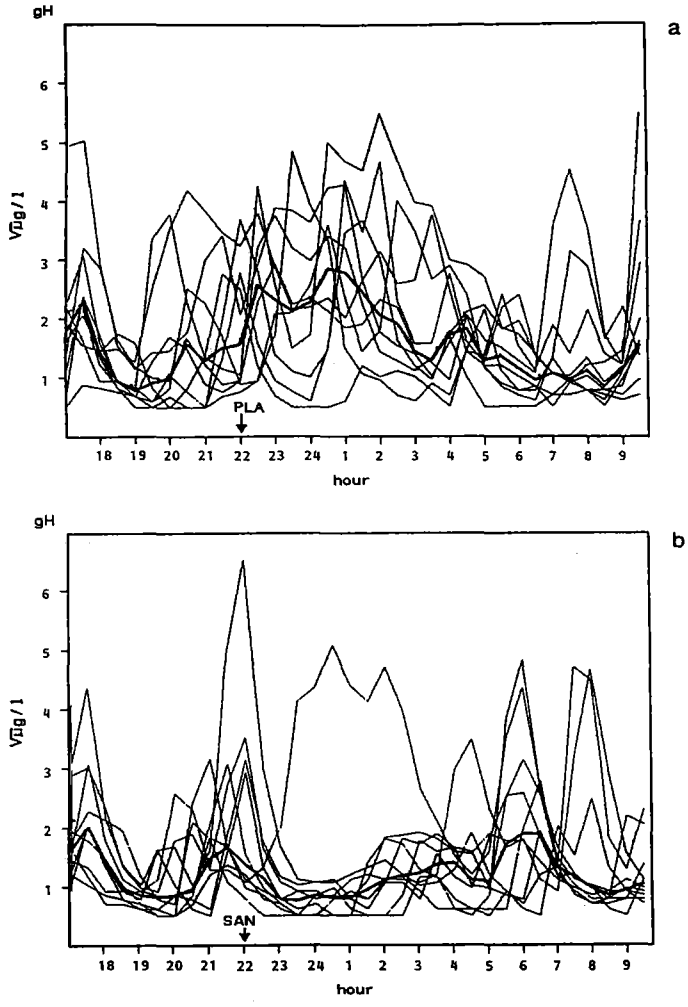

Figure 11 (a) Individual courses of GH after placebo (PLA) administration in teenage (n=10) type I diabetic patients. On the horizontal axis the hours and on the vertical axis GH expressed as the square root of the concentration in µg/l. **(b)** Individual courses of GH after 50µg sc octreotide (SAN) administration in the same group of teenage type I diabetic patients. The horizontal axis represents time (hours), while the vertical axis expresses GH as the square root of the concentration in µg/L. Bold line indicates mean blood glucose levels. Adapted from Aarsen RSR, Bruining GJ, Grose WFA, Van-Strik R, Lamberts SWJ, Harris AG[103].

administration in teenage patients with diabetes possibly argued against repeated bedtime administration of octreotide, as both are important sources of energy for the brain.
Serrano-Rios' et al demonstrated that after stabilising blood glucose by means of an artificial pancreas, octreotide and insulin were more effective than insulin alone in preventing nocturnal increases in blood glucose in nine often type I patients. Octreotide (100 µg sc at midnight) was administered with a continuous overnight insulin (0.15 mg/kg/min) and glucagon infusion (0.6 ng/kg/min)[104]. Glucagon, cortisol and C-peptide levels were similar in both regimens. Although bedtime (10pm - 11pm) administration of octreotide in other studies was associated with a

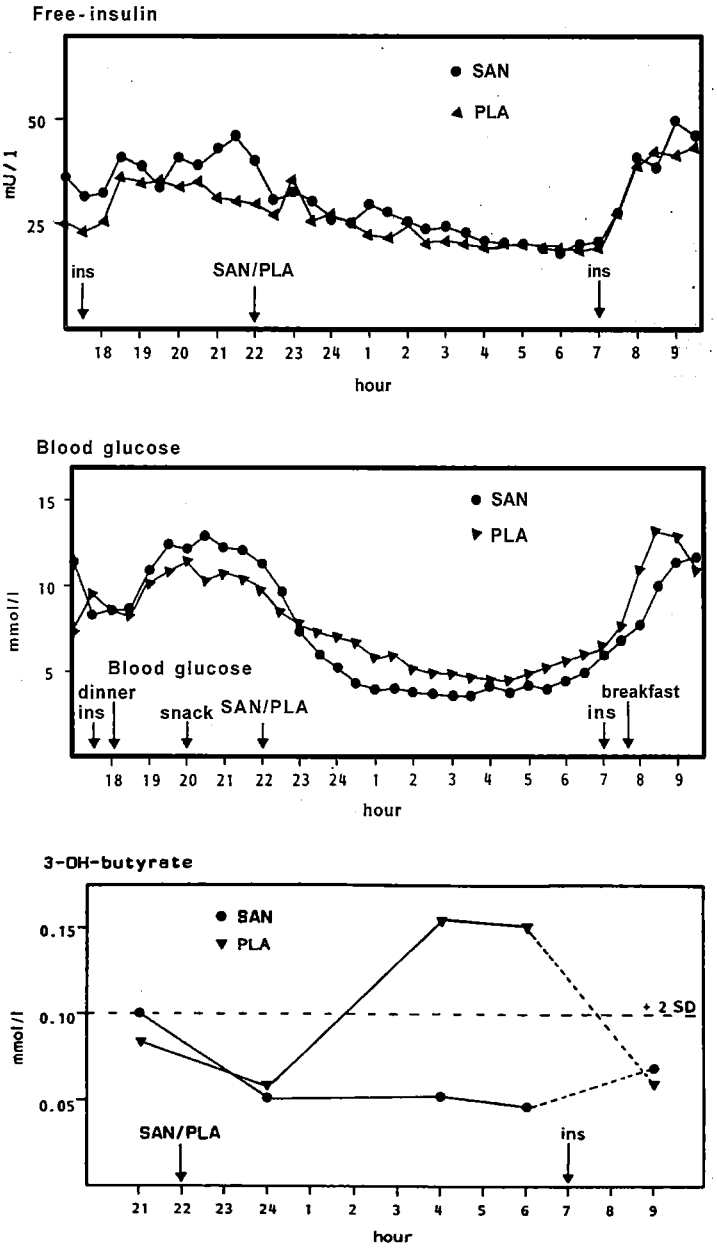

Figure 12.

Upper figure: Median courses of free insulin after either 50 µg sc octreotide (SAN) or placebo (PLA) administered at 10pm in 10 teenage type I diabetic patients. The horizontal axis represents time (hours) while the vertical axis represents the free insulin concentration in mU/L.

Middle figure: Median courses of blood glucose after either octreotide 50 µg sc (SAN) or placebo (PLA) administered at 10pm in 10 teenage type I diabetic patients. The horizontal axis represents time (hours) and the vertical axis the blood glucose concentrations in mmol/L.

Lower figure: Median courses of 3-OH-butyrate after either octreotide 50 µg sc (SAN) or placebo (PLA) administered at 10pm in 10 teenage type I diabetic patients. Hours are on the horizontal axis and the vertical axis represents the 3-OH-butyrate concentration in mmol/L. The dotted line represents the upper limit of normal values (±2SD). Ins=insulin. Adapted from Aarsen RSR, Bruining GJ, Grose WFA, Van-Strik R, Lamberts SWJ, Harris AG [103].

significant reduction of blood glucose and GH levels for 4 to 6 hours [105, 106, 107], octreotide failed to prevent early morning hyperglycaemia ("dawn phenomenon") and octreotide significantly reduced ketogenesis resulting from insulin deprivation [108].

With Scheen et al we studied the ability of octreotide to prevent the metabolic changes induced by a 6-h nocturnal arrest of an insulin pump [109]. Nine C-peptide negative Type 1 diabetic patients were submitted to two interruptions of a continuous s.c. insulin infusion, once after a single s.c. injection at 11.00 pm of 50 µg of octreotide and once a control (saline) injection. Plasma octreotide levels peaked at midnight and then declined with an elimination half-life averaging 144 ± 15 min. Plasma glucagon and growth hormone levels were significantly reduced after octreotide whereas the progressive fall in plasma-free insulin levels from 11pm to 5am was unaffected. In the control test, blood glucose levels tended to decrease slightly from 11pm to 2am and then increased markedly from 2am to 5am, while after octreotide they decreased significantly from 11pm to 2am. This resulted in blood glucose values below 3 mmol/L in seven subjects, but a secondary increase in glucose occurred up to 5am. Rises in plasma non-esterified fatty acid and glycerol levels were not reduced by octreotide, plasma 3-hydroxbutyrate levels were reduced late in the study (from 2am to 5am). We concluded that octreotide 50 µg sc significantly reduced the variations in plasma glucose usually seen during insulin interruption, although there was a higher risk of early hypoglycaemia.

Overnight Metabolic Profile Studies : Effect of Octreotide on the Dawn Phenomenon

As mentioned above, normal early morning GH surges were thought to be strongly associated with increased blood glucose and worsened control in diabetic patients. A group of studies were performed specifically to examine the effect of octreotide on glycaemic control during this so-called "dawn phenomenon". Type I diabetic patients underwent euglycaemic clamping to maintain blood glucose overnight, and also received a night-time dose of octreotide 50 µg s.c. Mean and peak GH levels were reduced during the early part of the night and morning insulin requirements were reduced in two studies. These euglycaemic studies then progressed to double blind placebo-controlled trials of 50 µg octreotide at bedtime, examining effects on overnight hormonal and metabolic profiles. Octreotide reduced GH and blood glucose for 5 hours post-administration, after which octreotide was fully metabolised. The low octreotide dose may have contributed to the fact that morning blood glucose readings were reduced in only 50% of patients. In addition to effects on glucose metabolism, octreotide also reduced overnight lipolysis and ketogenesis, without reducing circulating insulin. We proposed that chronic suppression of free fatty acid levels in adolescents could prove beneficial with regard to the development of atherosclerosis. These metabolic results clearly indicated to us that octreotide was well tolerated in type I diabetic patients and that pre-bedtime administration of octreotide could reduce

ketogenesis, lipolysis, GH and glucagon overnight. In confirmation of our findings, in a recent study of eight patients with type I diabetes Lunetta et al investigated the effectiveness of octreotide in controlling the "dawn phenomenon". All patients consistently experienced morning hyperglycaemia, and octreotide was administered as a subcutaneous injection at various times in the evening (50 μg at 8pm, 10pm or 12am), or as a continuous s.c. infusion from 12am to 8am with an increased rate between 3am and 8am. However, the authors found that infused octreotide provided greater control of overnight glucose (and GH) secretion than intermittent injections of octreotide [110].

Effects of Pre-meal Octreotide on Metabolic Control in Type I Diabetes

In a short-term administration study, Spinas et al reported in 1985 that octreotide 50-100 μg s.c reduced significantly post-prandial glucose concentration from 8.9 ± 0.7 to 7.8 ± 0.6 mmol/L ($p<0.001$) in patients with type I diabetes, while glucagon and triglyceride levels were also significantly reduced during a 180 minute period immediately after injection [111]. The acute effects of octreotide on insulin requirements in six patients with type I diabetes, who were connected to a feedback glucose-controlled insulin infusion system, have been studied by Hadjidakis et al [112]. Administration of octreotide 50 μg three times daily by s.c. injection resulted in a significant reduction in mean insulin requirements, GH and postprandial glucagon secretion during the 24 hours of observation. In a long-term study with Kirkegaard et al, we investigated the influence of octreotide treatment on glycaemic control in a controlled trial of 14 type I diabetes patients [113]. Seven patients received s.c. octreotide (initially 50 μg increasing in 50 μg increments every two days to a maximum of 400 μg/day for 12 months) and seven acted as controls. Overall, octreotide had no effect on metabolic control in Type I patients. Insulin requirements were reduced by approximately 25% and these returned to pre-treatment levels at the end of the trial. The frequency of daytime, but not nocturnal, low blood glucose values (<3.6 mmol/l) was significantly lower during octreotide therapy than after withdrawal ($p<0.02$). In a further study, which used a clamp technique, a 24-hour metabolic and hormone profile was performed before and after subcutaneously infused octreotide (200 μg/day for eight days) in six type I diabetes patients. Compared with baseline, octreotide suppressed 24-hour GH and glucagon levels, reduced insulin requirements, increased glucose storage and reduced energy expenditure [114]. Di Mauro et al compared subcutaneous intermittent octreotide with subcutaneous infusion (50 μg tid sc or 150 μg/24 hours) and reported significantly reduced daily glucose levels in seven type I diabetic patients with poor metabolic control [115]. GH levels were also reduced during octreotide treatment, but in contrast to other studies above no change in glucagon levels were seen. In a subsequent follow up study the same group reported that glucagon, GH and glucose were all reduced by subcutaneous injected and infused octreotide, with greater effects on glucagon being noticed at higher infused doses of octreotide [116]. Octreotide may reduce glucose levels by increasing the rate of oxidative but not non-oxidative glucose disposal [117]. Glucose storage as assessed by total glycogen synthase activity was not changed by octreotide.

III.IV.II.IV - Metabolic Effects of Octreotide in Type II Diabetes Mellitus

Given the complex pathophysiology of type II diabetes mellitus and the relative heterogeneity of patient characteristics, responses and disease severity, the results obtained from studies with octreotide in type II diabetes mellitus are diverse (*Table 2*).

Author	Octreotide dose (n)	Blood Glucose	C-peptide	Other Results
Haupt et al [124]	25μg tid (n=5)	Overall unchanged ↓ post breakfast	↓	
Verschoor et al [125]	12.5 μg tid (n=6)	↓	↓	
Rodier et al [126]	25 μg sc/iv (n=6) 8 mg po 30 min post meal	~	↓	
Anton et al [127]	50 μg iv (n=5) 30 min post meal		↓	
Davies et al [119]	50 μg 30 min pre meals	~	↓	
Williams et al [118]	50 μg tid (n=7)	Delayed pp rise in blood glucose	↓	↓ gg
Candrina et al [120]	100 μg insulin treated	↓ meal		
Giustina et al [121]	25, 50, 100 μg sc (n=11) insulin treated obese	↑ (ns)	↓	↓ gg

Table 2. Summary of studies detailing the metabolic effects of octreotide in patients with type II diabetes mellitus. ~ = unchanged, tid = three times daily, sc = subcutaneous, iv = intravenous, po = per os, ns = non-significant, pp = post prandial, gg= glucagon.

The effects of octreotide in doses of 5, 25, and 100 μg s.c. injected 30 minutes before a 530 kcal breakfast were studied by Williams et al from Prof. Bloom's group in 6 type II diabetic patients treated with diet and/or oral hypoglycaemic agents[118]. Octreotide decreased pre- as well as postprandial plasma levels of insulin by 50% with 5 μg; with 100 μg of octreotide, basal levels were suppressed by 75% with no postprandial rise at all. Basal glucagon was suppressed by 40% with 5 μg of octreotide. With 100 μg of octreotide basal levels of glucagon were reduced by 80% to a level that was maintained throughout the whole study period. Pancreatic polypeptide, gastrin, secretin and motilin were also suppressed by octreotide to a greater extent by 100 μg than by 5 μg. Glucose tolerance was not significantly changed by octreotide. Metabolic and hormonal effects of octreotide or placebo were also studied by Davies et al in 5 non-insulin-dependent diabetic patients on diet alone or diet with oral hypoglycaemic agents[119]. The 24-hour mean blood-glucose levels did not differ between the placebo and octreotide periods. In contrast to the Williams et al findings, the 24-hour mean insulin and glucagon levels were not significantly reduced, however at many individual time points significant reductions in both were seen. Blood lactate, pyruvate concentration, as well as 24 hour mean levels of glycerol and 3-hydroxybutyrate were not changed by octreotide.

In five patients with Type II diabetes with secondary failure of oral agents, octreotide 100 μg s.c. twice daily plus insulin produced a lowering of plasma glucose, plasma glucagon and serum C-peptide levels[120]. The same group studied the effects of single doses of octreotide on the glycaemic response to a mixed meal in 8 insulin-treated type II diabetic patients[121]. All patients underwent simultaneous treatment with insulin (0.1 U/kg s.c.) and octreotide (25 μg, 50 μg or 100 μg s.c.), followed by a standardized pre-constituted mixed meal. Following insulin alone, a significant increase in blood glucose levels after the meal was observed. Blunted blood glucose responses to the meal after each of the three doses of octreotide as compared to insulin alone were observed. It should be noted, however, that the confounding effect of concomitant insulin makes the precise interpretation of the activity of octreotide in these patients very difficult. More recently, Spanti et al. reported that octreotide at a dose of 150 μg per day as continuous infusion reduced insulin requirements but did not significantly reduce blood glucose in six type II diabetic patients with chronic renal failure who required insulin treatment[122]. This effect may have been mediated by a reduction in circulating glucagon. The same group also noted divergent metabolic effects in type I and type II diabetic patients treated with octreotide 100 μg per day for 5 days in a euglycaemic clamp study[123]. The type II diabetic patients experienced no change in glycaemic control or hepatic glucose production (in contrast to type I patients), despite lowered GH profiles. The authors suggested that a temporary reduction in insulin secretion (assessed via decreased C-peptide secretion) mediated by octreotide may have blunted glycaemic effects of octreotide in this euglycaemic clamp model.

Conclusion : Metabolic Effects

The relative heterogeneity of results with respect to GH suppression and glycaemic control across type I and type II diabetic patients made it difficult for us to interpret data during the Clinical Development Program. Before attempting to draw any definitive conclusions from the data generated from these diabetes studies, we emphasized that several confounding factors hampered the interpretation of these results in both type I and type II diabetes patients. The pathophysiology of type II diabetes is more complicated than that of type I diabetes because the entity is heterogeneous and characterized by both an impairment of beta cell function and diminished tissue sensitivity to insulin. Speculation persists about which of these two effects initiates the process. In both Type I and Type II the effects of octreotide on digestion, absorption and disposal of nutrients are also complex. Octreotide inhibits most of the peptide hormone secretions from the gut and pancreas. Suppressing several of these hormones simultaneously obviously interferes with the interpretation of glycaemic control data. In particular, the balance between suppression of insulin on one hand and of the anti-insulin counter-regulatory hormones GH and glucagon on the other depends upon the physiological importance of each of these hormones postprandially.

Other important issues include patient compliance in terms of ascertaining drug administration during the ambulatory phase of the study and the validity of capillary blood values reported by patients. Also the order in which drug or placebo are given in cross over designed studies is crucial because of the beneficial effect hospitalization itself has on blood glucose control.

From the data available, although fairly well tolerated, octreotide showed limited beneficial effects on glucose homeostasis. Yet it is interesting that octreotide did not cause significant deterioration in glucose tolerance in type II diabetes patients contrary to normal subjects who experienced impaired glucose tolerance suggesting that relative insulin suppression caused by octreotide is overridden by inhibition of counter-regulatory hormones which may play an important role in type II diabetes. Unfortunately, the balance between these opposing actions of octreotide in type II diabetes remains to be clarified.

We fostered an active discussion between study leaders to ascertain the direction of future studies with octreotide in diabetes at an investigators conference under the aegis of Sandoz. From their advice we concluded that octreotide did not cause hypoglycaemia in diabetes mellitus and the gastrointestinal hormone effects were tolerable and safe. Also, octreotide had a beneficial effect on hormonal profiles and glucose metabolism over acute and 24-hour administration, but the magnitude of this effect was moderate and heterogeneous across different studies. We believed that larger clinical trials would be needed to assess the clinical relevance of octreotide on glycaemic control in diabetes.

III.IV.III - Octreotide: Effect on Complications of Diabetes Mellitus

Diabetic Nephropathy

During the clinical development of octreotide in diabetes mellitus we performed and fostered numerous studies into its effect on diabetic nephropathy in animal and human studies.

Animal Studies

Rodent models of experimental (streptozotocin-induced) diabetes showed that octreotide (100 µg bid) reduced initial renal hypertrophy possibly via inhibition of renal IGF-1 accumulation[128]. We showed that lower dose octreotide only partially reduced kidney IGF-1 and renal growth, indicating a dose-response effect. With Allan Flyvbjerg and colleagues we studied the effect of longer-term octreotide treatment (100 µg bid for 6 months) in streptozotocin-induced diabetic rats in comparison with untreated rats (*Figures 13, 14*)[129]. Untreated diabetic and non-diabetic animals were used as reference groups. No differences were seen between the two diabetic groups in respect to body weight, food intake, blood glucose levels, urinary glucose output, haemoglobin A1C, fructosamine, serum growth hormone or creatinine clearance, but kidney weight, urinary albumin excretion, kidney and serum IGF-I were all reduced in the octreotide-treated diabetic animals when compared to the untreated diabetic group. In non-diabetic rats octreotide reduced body weight, kidney weight, urinary albumin excretion, kidney and serum IGF-I and serum GH compared to untreated controls. When kidney weights were expressed in relation to body weight no difference was found between octreotide-treated and untreated non-diabetic controls, while the difference between octreotide-treated and untreated diabetic animals was still significant. In conclusion, chronic administration of octreotide reduced diabetic renal hypertrophy and urinary albumin excretion. These results are interesting in light of the findings (*see below*) in the section on human studies, where a significant effect on renal size in type I diabetic patients was seen with three months of octreotide therapy, but not with nine months' treatment with another somatostatin analogue, lanreotide. It could be that tolerance to the effects of somatostatin analogues develops and early renal hypertrophy may therefore be IGF-1 dependent and amenable to octreotide therapy, while established diabetic nephropathy may be governed by other mechanisms.

The choice of animal model may also influence significantly the applicability of data to the effect of octreotide on diabetes in humans. As noted above, Flyvbjerg and colleagues have performed a series of experiments in diabetic rats. It may be, however, that their work in mice is a more accurate model of human endocrine dysregulation in diabetes[130], as the main rat model, namely the streptozotocin-induced diabetic rat, displays GH suppression in contrast to the GH hypersecretion seen in humans and in mice[131]. In a practical sense murine models may be more useful to study diabetes given

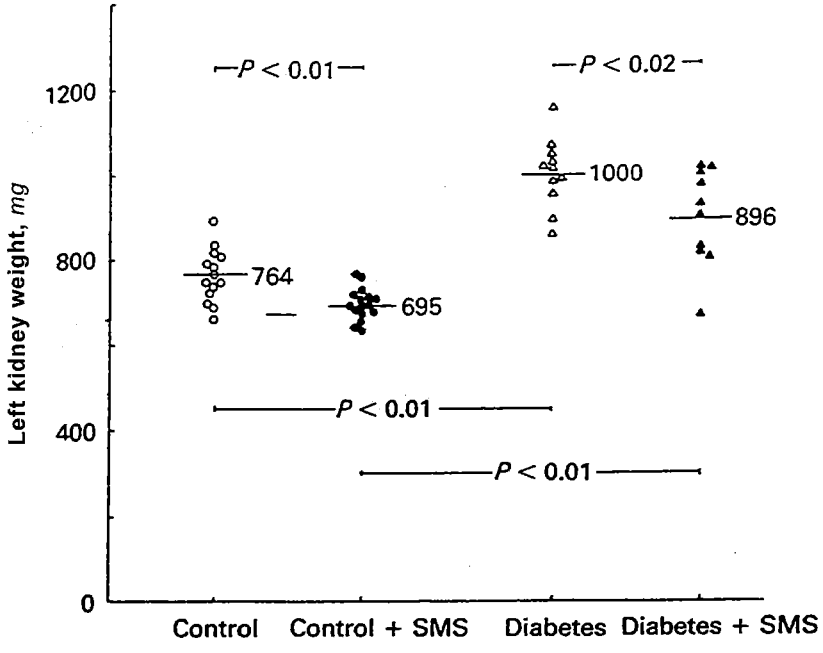

Figure 13. Individual kidney weights in each of four groups of rats (control and streptozotocin-induced diabetic; treated or untreated with octreotide (100 µg bid)) at the end of 180 days treatment with octreotide. Mean values for each group are indicated by a horizontal bar. Octreotide treatment was associated with significantly lower kidney weight than non-octreotide treated control animals and diabetic animals. Statistical significance between groups are as indicated in the figure. SMS = octreotide. (Adapted from Flyvbjerg A, Marshall SM, Frystyk J, Hansen KW, Harris AG, Orskov H[129]).

that they have a 10-times lower body weight than rats and their relatively short growth and development cycle means that practical data may be generated using models of only one months' duration, such as that of Van Neck et al [132].

Human Studies

Human studies of diabetic nephropathy during the clinical development program were limited in scope as retinopathy and metabolic control were the primary targets of research. An important factor in the development of diabetic nephropathy is glomerular hyperfiltration. The importance of regulatory peptides in renal failure has been described [133]. The effect of octreotide on kidney function has been evaluated in type I diabetes patients; a significant decrease in glomerular filtration rate (GFR) was noted in some studies [134] but not in others [135]. We investigated the renal response to increasing doses of octreotide (50, 100 and 200 μg/day over 3 days), in seven insulin-dependent diabetic patients without microalbuminuria, with Poirier et al [136]. Reduction of GFR was marked in four of the patients, of whom three fell into the normal range. Two patients also had a simultaneous reduction of renal plasma flow (RPF), but there were no significant changes in GFR, renal plasma flow or filtration fraction in three patients, including two who had high GFR initially. Similarly, Christensen et al. also found that constant i.v. infusion of octreotide 8 μg/hour acutely reduced renal hyperperfusion and hyperfiltration in 10 patients with insulin-dependent diabetes [137].

Stegeman et al reported that the acute renal effects of octreotide (20 μg bolus, then 10 μg/hour i.v.) were antagonised by glucagon (2-3 ng/kg weight/minute) in 13 insulin-dependent diabetic patients [138]. Administration of octreotide alone led to significant decreases in both glomerular filtration rate and effective renal plasma flow (by 6.3 ml/min/1.73 m^2 and 43.9 ml/min/1.73 m^2, respectively, compared with baseline ($p<0.001$). Urinary flow, free water clearance and sodium excretion were also reduced during octreotide infusion. Administration of glucagon in addition to octreotide completely abolished these reductions. The authors suggested that octreotide and glucagon might functionally antagonise one another's acute effects on renal dynamics in diabetic patients.

Octreotide infusion in type I diabetic patients reduced renal plasma flow and glomerular filtration rate, which are elevated in early diabetic renal disease [139]. Plasma GH and glucagon fell in these patients and the fall in glucagon was statistically correlated with the decrease in renal plasma flow and glomerular filtration rate. With Serri et al, we performed a 12-week study with octreotide in human diabetic nephropathy; octreotide was administered by continuous s.c. infusion (300 μg/day) for 12 weeks [140]. Octreotide was safe and well tolerated and caused no hypoglycaemia. A number of metabolic and renal benefits were noted. Insulin requirements fell during the study without any worsening of glycaemic control, possibly via an increase in insulin sensitivity. GH secretion was not significantly affected by octreotide, but IGF-1 fell significantly through-

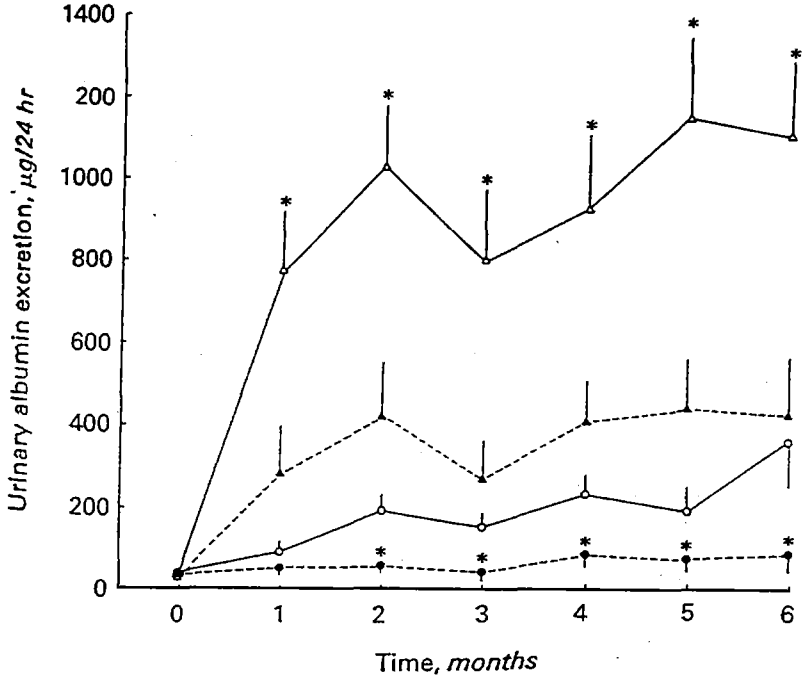

Figure 14. Changes in urinary albumin excretion over six months in non-diabetic rats with (●) or without (○) octreotide (100 μg bid) and in steptozotocin-induced diabetic rats with (▲) or without (△) octreotide. Data are expressed as means (SEM. *Octreotide treatment was associated with significantly lower urinary albumin excretion than non-octreotide treated groups. $P<0.05$ octreotide treated animals versus all other groups. (Adapted from Flyvbjerg A, Marshall SM, Frystyk J, Hansen KW, Harris AG, Orskov H [129]).

out the study (*Table 3*). The reason for this disconnect is not known, although serum IGF-1 levels could have been affected by an octreotide-induced increase in IGFBP's. Renal hyperfiltration was reduced in the octreotide group (136 mL/min/1.73m²) compared with placebo (157 mL/min/1.73m²) (*Table 4*). Kidney hypertrophy was also lower with octreotide compared with placebo (379 mL/1.73m² versus 389 mL/1.73m²) (*Figures 15, 16*). Despite the clear-cut benefits of octreotide in experimental and human diabetic nephropathy, large-scale clinical trials were not performed. It is noteworthy that a subsequent longer study of lanreotide failed to show a substained reduction in glomerular filtration and IGF-1 after 9 months of treatment[141]. The advent of angiotensin converting enzyme (ACE) inhibitors coincided with the Clinical Development Program for octreotide. The proven benefit of ACE inhibitors in reducing renal albumin excretion, progression of nephropathy to dialysis and progression to transplantation effectively ended further interest in octreotide in this regard for pragmatic reasons. A safe effective oral therapy such as captopril thus had enormous benefits over octreotide in terms of compliance, and costs were significantly lower.

Diabetic Retinopathy

In vitro studies indicated that octreotide inhibited new vessel growth and endothelial cell replication[142]. The initial human study performed by Kohner's group in London in proliferative and pre-proliferative diabetic retinopathy treated nine type I patients with octreotide at doses up to 1500 µg per day remained unaffected[143]. No worsening of glycaemic control was seen, but GH suppression was incomplete with three times per day intermittent injections and a subcutaneous pump study (500 µg/day) was instituted in six of the nine patients. Although GH was not fully suppressed in this trial, IGF-1 levels fell into the hypopituitary range and insulin requirements were cut by 50%. Clear improvements in diabetic retinopathy were seen in individual patients, but these changes were heterogeneous. Furthermore, the small patient numbers did not provide evidence of dose-responses. In another study we performed with Shumak and Zinman et al in type I diabetes patients with background retinopathy, the picture was also unclear, as octreotide provided no reduction in disease severity (microaneurysm formation, capillary leakage) compared with placebo[144]. However visual activity improved significantly in right ($p<0.05$) and left eyes ($p<0.03$) in six type I diabetes patients treated with octreotide for eight weeks and retinopathy improved in two of these subjects. GH levels and insulin requirements fell significantly during octreotide treatment. Similar results were obtained in another pilot study of six type I diabetes patients, three who underwent hypophysectomy and three who received octreotide (400 µg/day by CSI for 9-18 months). In the former group, GH levels were undetectable and the ocular condition improved rapidly. After octreotide, GH levels fell by 50%, the patients' retinopathy was stabilised and there was improvement in visual acuity[145]. Important studies of octreotide in diabetic retinopathy are outlined in Table 5.

Treatment Group	Placebo (n=6)	Octreotide (n=5)	P†
Glucose level, (mmol/L)			
Baseline	11.7 ± 0.7	8.7 ± 0.8	.030
Week 3	11.2 ± 1.7	10.9 ± 1.7	.895
Week 12	10.7 ± 0.3	10.1 ± 0.8	.533
Glucagon level, (ng/L)			
Baseline	145 ± 16	113 ± 9	.095
Week 3	153 ± 4	102 ± 20	.699
Week 12	135 ± 10	106 ± 16	.735
Growth hormone level, (µg/L)			
Baseline	3.05 ± 0.64	2.5 ± 0.4	.622
Week 3	3.24 ± 0.65	1.84 ± 0.25	.095
Week 12	3.13 ± 0.64	2.58 ± 0.45	.735
Insulin-like growth factor-I, (U/mL)			
Baseline	0.91 ± 0.14	0.96 ± 9,17	.792
Week 3	0.99 ± 0.19	0.50 ± 0.12	.000
Week 12	0.91 ± 0.14	0.57 ± 0.10	.001
Glycosylated haemoglobin level, (%)			
Baseline	0.11 ± 0.01	0.12 ± 0.005	.247
Week 12	0.11 ± 0.01	0.11 ± 0.01	.420
Daily Insulin dose, (U)			
Baseline	55 ± 10.9	63 ± 7.2	.329
Week 12	55.3 ± 8.9	41.6 ± 4.2	.002

Table 3. Metabolic and hormonal parameters before and after treatment with octreotide or placebo in patients with insulin-dependent diabetes mellitus. Values are mean ± SE. † Baseline comparison of placebo and octreotide groups was made using the Mann-Whitney U test. Week 3 and 12 comparison of placebo and octreotide groups, controlling for baseline values, were made using nonparametric analysis of covariance (Adapted from Serri O, Beauregard H, Brazeau P, Abribat T, Lambert J, Harris A, Vachon L[140]).

Treatment Group	Placebo (n=6)	Octreotide (n=5)	P†
Glomerular filtration rate, (mL/min per 1.73m²)			
Baseline	159 ± 5	173 ± 15	.662
Week 12	157 ± 7	136 ± 12	.037
Kidney volume, (R+L, mL1/1.73 m²)			
Baseline	384 ± 18	426 ± 42	.429
Week 12	389 ± 18	379 ± 30	.047

Table 4. Glomerular filtration rate and kidney volume before and 12 weeks after treatment with octreotide or placebo in patients with insulin-dependent diabetes mellitus. Values are mean ±SE. †Baseline comparison of placebo and octreotide groups was made using the Mann-Whitney U test. Week 12 comparison of placebo and octreotide groups was made controlling for baseline values using nonparametric analysis of covariance. (Serri O, Beauregard H, Brazeau P, Abribat T, Lambert J, Harris A, Vachon L[140]).

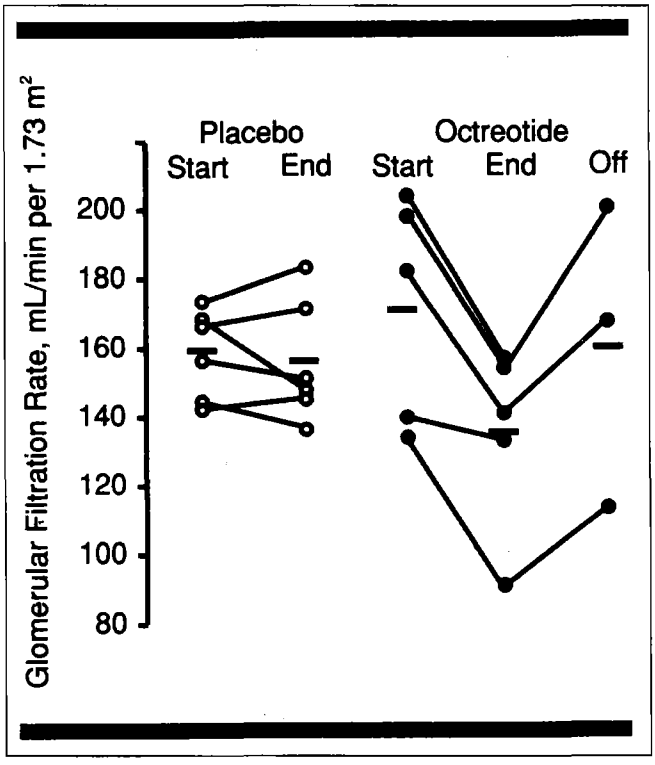

Figure 15. Individual values for glomerular filtration rate in placebo (n = 6) (open circles) and octreotide (n = 5; 300 µg/24hours) (closed circles) treatment groups at the start and end of 12 weeks' treatment and after cessation of octreotide therapy (Off) in type I diabetic patients. Mean glomerular filtration rate was significantly lower (P = 0.037) in the octreotide-treated group compared with placebo-treated patients. The horizontal bars indicate mean values. (Serri O, Beauregard H, Brazeau P, Abribat T, Lambert J, Harris A, Vachon L[140])

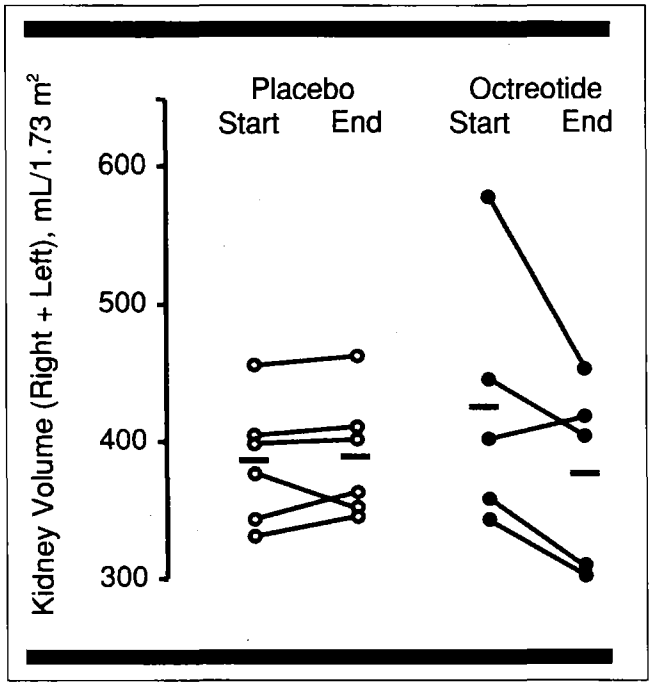

Figure 16. Individual values for kidney volume in placebo (n = 6) (open circles) and octreotide (n = 5; 300 µg/24hours) (closed circles) treatment groups at the start and end of 12 weeks' treatment and after cessation of octreotide therapy (Off) in type I diabetic patients. Mean kidney volume was significantly lower (P = 0.047) in the octreotide-treated group compared with placebo-treated patients. The horizontal bars indicate mean values. (Adapted from Serri O, Beauregard H, Brazeau P, Abribat T, Lambert J, Harris A, Vachon L[140]).

REFERENCE	PATIENT POPULATION	TREATMENT	RESULTS
Hyer et al[143]	8 PR 1 PPR	500 µg /d-1500/d 2-20 weeks	No effect
Shumak et al[144]	6 NPR	50-150 µg /d CSI, SC 8 weeks	2 patients improved (angiograms)
Kirkegaard et al[113]	7 early PR	400 µg/d CSI for 12 months	No effect
Mallet et al[145]	4 PR	400 µg /d CSI 6-20 months	2 patients stabilized 2 patients had regression of neovascularisation
Luettke et al[146]	5 PR type 1 diabetes 4 PR type 2 diabetes	300 µg /d sc 12-36 months	Significant reduction hemorrhage vitreous Regression neovascularization
Grant et al[168]	8 severe NRP	200-5000 µg /day CSI for 15 months	1/22 eyes vs. 9/24 eyes control reached high risk ocular disease progression 27% OCT vs. 42% Control decreased IGF-1

Table 5. Summary of clinical studies on the effect of octreotide on diabetic retinopathy. PR = proliferative, PPR = preproliferative, NPR = non proliferative; ON = ocular neovascularization, CSI = continuous subcutaneous infusion, GH = growth hormone, IGF-1 = insulin-like growth factor-1, OCT = octreotide, sc = subcutaneous, HbA1c = haemoglobin A1c.

The results of clinical trials with octreotide in diabetic retinopathy were discussed in 1988 with a group of experts. With octreotide treatment GH and IGF-1 levels were not fully suppressed at the doses used. This prevented the conference from making a clear-cut finding regarding the importance of GH/IGF-1 in diabetic retinopathy and by extension the possible therapeutic role of octreotide. It was concluded that since GH and IGF-1 play a partial role in the pathogenesis of diabetic retinopathy, octreotide might reduce disease severity by inhibiting neovascularisation. It was recommended that prospective dose-response trials be performed to ascertain whether complete GH suppression could be achieved with acceptable patient tolerability and safety. These trials would then have to be followed by large prospective clinical trials of octreotide in diabetic retinopathy. Despite the apparent lack of success of the clinical development program in diabetes, the results we obtained have to be re-evaluated in the light of subsequent studies with octreotide the availability of a once a month slow release preparation of three dosage strengths of octreotide LAR (10, 20, 30 mg) and the advances in understanding of the pathophysiology of diabetic complications.

III.V - REVIEW OF THE IMPACT OF OCTREOTIDE RESEARCH IN DIABETES MELLITUS

Many of the clinical trials that we instigated during the clinical development program were continued and published by our collaborating investigators. In particular, studies regarding the effects of octreotide on diabetic retinopathy have continued and important evidence has accumulated.

III.V.I - Metabolic Effects of Octreotide

There have been conflicting reports about the efficacy of octreotide in the reduction of postprandial hyperglycaemia [147,148]. Divergence in reported results may be due to inter-subject variability in the severity of diabetes, or, as suggested by the work of Osei et al, minor variability in the in vivo metabolism of octreotide during 24-hour continuous subcutaneous infusion (as assessed by inter-individual variations in trough, mean and peak plasma octreotide concentrations at steady state) [149]. Octreotide 50 μg s.c. tid for eight weeks decreased mean insulin requirements in six patients with type I diabetes, although there was no change in the 24-hour glucose profiles [150]. Nosari et al, showed significant reductions, compared to placebo, in postprandial glycemic peaks ($p<0.05$), insulin requirements ($p<0.01$), glucagon ($p<0.05$) and GH levels ($p<0.05$) in 8 type I patients receiving octreotide 50 μg sc at 1pm plus a standardised meal [151]. However, chronic administration of octreotide 10 or 50 μg twice daily for four weeks to 26 patients with type I diabetes did not appear to improve overall metabolic control [111]. The authors speculated that administration of higher doses of octreotide by continuous s.c. infusion would avoid dose-limiting gastrointestinal side effects and produce GH and glucagon suppression.

Patients with type II diabetes comprise almost 90% of all diabetic patients, and only 10% of these achieve adequate glycemic control through dietary measures alone. It is estimated that 11% to 36% of type II patients no longer respond to diet and sulfonylurea therapy after one year of treatment [152]. Patients who develop failure to sulfonylureas usually require exogenous insulin to overcome their metabolic insulin resistance. Often treatment with insulin alone or combined insulin-sulfonylurea provides sub-optimal long-lasting satisfactory metabolic control [153] and may contribute to worsening obesity.

Orskov et al have studied the effect of continuous subcutaneous octreotide, in type II diabetic patients. After only four days of continuous octreotide therapy (1 μg/kg/day), decreased insulin requirements, increased insulin sensitivity (in the form of increased peripheral glucose disposal and increased suppression of hepatic glucose output) and increased oxidative glucose disposal could be demonstrated [154]. Subcutaneous pre-meal octreotide (50 μg s.c.) reduced [155] or delayed [156] post-prandial glycaemic peaks in type II diabetic patients. Octreotide (50 μg s.c.) has also been reported to inhibit insulin secretion without a deterioration of glycaemic control [157, 158, 159]. In five type II patients with secondary failure of oral therapy, octreotide 100 μg sc twice daily plus insulin produced a lowering of plasma glucose, plasma glucagon and serum C-peptide levels, suggesting that octreotide may lead to a reduction of daily insulin requirements and have a role as an adjunct to insulin in type II diabetes after failure of oral hypoglycaemics [115].

Overall, the results with octreotide in metabolic control of type I and type II diabetes during and after the Clinical Development Program have been mixed. Treatment with octreotide was not associated with a major increase in hypoglycaemia in type I or type II patients. Indeed, in patients with suphonylurea overdose, octreotide has been recommended as a valid emergency room treatment for hypoglycaemia [160]. Interest in octreotide in diabetes mellitus waned in the late 1980's as the dawn phenomenon fell out of favour as a major mechanism for poor glycaemic control. Also, the publication of the DCCT trial shifted the focus of diabetologists to maximizing insulin therapy to achieve near-normal HbA1c when appropriate in type I patients. The subsequent publication of the UKPDS trial in type II diabetes in the late 1990's provided firm evidence for tight blood glucose and blood pressure control as effective interventions [161]. The practicality of adding octreotide to the treatment regime for patients with diabetes already on multiple medications raises major compliance issues. It remains to be seen how well current therapy with insulin, oral hypoglycaemics and insulin sensitising drugs reduce complications over the longer term. Indeed, some poorly responsive sub-groups may benefit from octreotide as an add-on therapy, especially as the clinical development program conducted intensive safety studies. This may pave the way for the eventual study of once monthly depot octreotide long acting repeatable (LAR) or newer more potent and more subtype receptor specific somatostatin analogues in the metabolic control of diabetes mellitus.

III.V.II - Effect of Octreotide on Diabetic Complications

While interest in the role of octreotide as a treatment for metabolic and nephropathic disturbances decreased with the advent of new guidelines recommending intensified insulin therapy and ACE inhibitor therapy, pre-clinical and clinical research continues in diabetic retinopathy. In 1997, Smith et al reported that GH is essential for retinal neovascularisation in mice in response to ischaemia[162]. This study used transgenic mice that expressed dwarf (GH-antagonist) and giant (GH-agonist) phenotypes and retinal neovascularisation was induced by hypoxia/reperfusion similar to retinopathy of prematurity. GH antagonist expressing mice had reduced levels of revascularisation compared with normal controls, although GH agonist mice had no increased degree of retinopathy compared with controls. Non-transgenic mice were treated with a somatostatin analogue, MK 678, and this reduced retinal revascularisation by 44 % compared with controls. Interestingly this anti-angiogenic effect was dose-related and linear regression analysis demonstrated that neovascularisation was correlated strongly with IGF-1 concentration. The importance of GH in neovascularisation was shown subsequently by co-administering GH and MK678 in normal mice. Compared with controls, GH suppressed/replaced (MK 678 plus GH) mice had increased retinal neovascularisation. Furthermore, replacement of IGF-1 in somatostatin analogue treated mice restored retinal neovascularisation to control levels, although exogenous IGF-1 alone did not increase retinopathy. These results suggest that GH is a vital facilitator of hypoxia-induced retinal neovascularisation, and that its actions are mediated in part by IGF-1. Blockade of the GH-IGF-1 axis by transgenic GH antagonist expression or somatostatin analogue administration did not abolish neovascularisation fully, however. Vascular endothelial growth factor (VEGF) is another important growth factor in retinal neovascularisation, and GH/IGF-1 axis modulation did not alter VEGF dynamics in this model. Despite the fact that this was an animal model of hypoxia-induced retinopathy (not diabetic retinopathy), some importance of GH/IGF-1 in retinal neovascularisation in diabetic humans can be inferred, especially in combination with the other data outlined above.

The precise role of GH, IGF-1 and IGFBP's in diabetic angiopathy, however, remains to be resolved. Evidence exists in the literature both in favour and against a stimulatory role for IGF-1 in diabetic retinopathy. While Merimee reported elevated IGF-1 levels in a small number of patients with progressive retinopathy[13], a recent review has pointed out that the statistical analysis used in the Merimee series may not be valid[25]. Other studies have not confirmed Merimee et al's observations, with a large study finding that IGF-1 levels were not predictive of developing retinopathy over a six-year follow-up[163]. Much of the continuing uncertainty regarding the role of the GH/IGF-1 axis in diabetes may be apportioned to the unknown relative effects of tissue and circulating changes in IGF-1 and its binding proteins in response to hyperglycaemia.

Smith et al have recently reported that an IGF-1 receptor antagonist suppresses retinal neovascularisation in a mouse model of ischaemia induced proliferative retinopathy[164]. They also proposed that interactions between IGF-1 and IGF-1 receptor may be necessary for maximal induction of neovascularisation by VEGF and that increased IGF-1 levels are likely to promote retinal neovascularisation by supporting VEGF-induced endothelial cell proliferation. Hellstrom recently demonstrated that low IGF-1 levels suppress VEGF surviving signalling, with retinal endothelial cells acting as a permissive factor for maximum VEGF stimulation of angiogenesis[165]. These data from patients with Laron-type dwarfism (GH receptor and IGF-1 allelic mutations) provide the first genetic evidence for a role of the GH-IGF axis in normal retinal vascularisation in humans and adds significantly to the body of data supporting a role for IGF-1 in diabetic retinal neovascularisation.

Grant et al have previously shown that human retinal endothelial cells (HRECs) have somatostatin receptors and that octreotide decreases the proliferation of HRECs in response to IGF-1 and fibroblast growth factor[166]. Grant proposes the theory (personal communication) that somatostatin analogues acting as anti-angiogenic agents for the treatment of proliferative diabetic retinopathy may mediate their growth inhibitory effects on HRECs in part by increasing IGFBP-3 expression. In a rat study, octreotide was found to acutely stimulate hepatic IGFBP-1 and IGFBP-3 mRNA in vivo, which may represent a relevant form of IGF-1 regulation, although similar studies have yet to be performed in retinal tissue[167]. Until these complex interactions between IGF-1 and IGFBP's are defined more precisely the relative merits of research findings will be obscured.

Despite the pathophysiological uncertainty, clinical trials with somatostatin analogues in retinopathy have continued. In 2000, Grant and colleagues published a study with high-dose octreotide 168. From the safety studies during and after the clinical development program in acromegaly and gut endocrine tumours, it had been demonstrated that high-doses of octreotide are safe and relatively well tolerated. Grant et al studied the effects of maximally tolerated doses of 200 - 5000 µg/day of octreotide via continuous sc infusion for 15 months in 11 patients with severe non-proliferative diabetic retinopathy compared 12 with control patients. Octreotide treatment was well tolerated and no patient dropped out of the study early. The endpoint was development of high-risk proliferative diabetic retinopathy in an eye. Only one of 22 eyes in the octreotide group developed proliferative retinopathy, requiring photocoagulation compared to 9 of 24 eyes in the control group. Considered independently, this was statistically significant ($p = 0.006$), although the overall treatment effect was not ($p = 0.0605$). The incidence of patients with disease progression to severe proliferative diabetic retinopathy was 9% in the octreotide treated patients compared with 42% in the conventionally managed control group during the 15-month study period. HbA1c improved with octreotide therapy from 8.3 ± 0.8% to 7.1 ± 0.6 % while no change was seen in the control group. IGF-1 secretion fell by 50% in the octreotide group ($p<0.05$), but was essentially unchanged in controls. As this was a pilot study, the authors were cautious about extrapolation of their results.

Boehm et al administered 100 µg octreotide sc tid for a maximum of 36 months to nine patients with type I (n=5) or type II (n = 24) diabetes and high-risk proliferative diabetic retinopathy [169]. Nine patients served as controls. Neovascularization decreased in 12 of 14 eyes (86%) and remained stable in 2 of 14 eyes (14%). In the control group, neovascularization worsened in 5 of 12 eyes and remained stable in 7 of 12 eyes (58%). Vitreous haemorrhage occurred in 10/14 eyes (7%) in the octreotide treated patients and in 5 of 12 eyes (42%) in the control groups. None of the patients needed vitrectomy in the octreotide population compared to 3 (25%) in the control group. HbA1C remained unchanged in the octreotide treated patients and insulin requirements were reduced by up to 50%.

Somatostatin subtype receptors SST2A and SST3 have been described in the human retina establishing that these receptors are synthesized in the human retina. In vitro SST expression in ischemic retinas from diabetic retinopathy patients was investigated by van Hagen et al and others [170,171]. They found sporadic expression in non-proliferative and variable expression in early proliferative and end stage proliferative ischaemic retinal disease. Intraretinal neovascularisations stained generally negative and pre-retinal neovascularisations stained variably positive. In end stage pre-retinal vascularizations, variable but marked positive staining was detected in the pre-retinal membranes. The authors suggest, based on this data, that the anti-angiogenic effects of somatostatin analogues may be limited. This was confirmed by pilot studies showing a limited effect of octreotide in non-proliferative diabetic retinopathy and a more beneficial effect of the analogue in advanced proliferative diabetic retinopathy following extensive laser therapy. The development of somatostatin analogues with greater selectivity for somatostatin receptor subtypes 2 and 3 may thus provide greater control of retinal neovascularisation.

With reference to the original recommendations of the NIH regarding retinopathy and octreotide in 1988, it appears that large-scale trials may be both feasible and warranted. Indeed, the recognized safety of high-dose octreotide would facilitate this process by obviating the need for a preliminary dose-ranging study.

Conclusion

In the time that has passed since the completion of the diabetes mellitus phase of the Clinical Development Program for octreotide, the complex pathophysiology of the disease and its complications has become even more apparent. Despite the advances in genetics and molecular biology that have revolutionized diabetology in the last decade, we are far from a full understanding of the cellular mechanisms behind tissue damage in diabetes. Evidence has accrued from epidemiological population studies regarding the heavy impact of diabetes mellitus on morbidity and mortality, and it remains an important risk factor for cardiovascular disease and stroke [172]. Of great concern is the rising incidence of type II diabetes mellitus in developed and developing countries, which appears to be mirrored by near-epidemic rates of obesity. The direct and indirect impacts of chronic hyperglycaemia and insulin resistance on the endothelium in large and narrow calibre vessels are significant [173]. The metabolic or insulin resistance syndrome comprises a complex of metabolic risk factors, including obesity (body mass index >25), hypertriglyceridaemia (>1.69 mmol/L), low high-density lipoprotein levels (<1.04 mmol/L in men; <1.29 mmol/L in women), hypertension, impaired glucose tolerance and family histories of type II diabetes mellitus, cardiovascular disease and polycystic ovary syndrome. These factors combined with complex issues such as a sedentary lifestyle and ethnicity combine to account for an increased risk of type II diabetes mellitus, cardiovascular disease and stroke in up to a third of people in the United States [174,175,176]. The metabolic/insulin resistance syndrome has risen in incidence by over 60% in the time since the Clinical Development Program for octreotide in diabetes mellitus was concluded [177]. Given the increasing impact of particularly type II diabetes mellitus, it is unfortunate that, apart from the glitazones, no new class of medications has become available to clinicians for the treatment of metabolic disturbances and complications. It is instructive, therefore, to reflect on the Clinical Development Program for octreotide as a roadmap for how testing of future anti-diabetic therapies might proceed.

Our overriding concern during the clinical development of octreotide was to maintain a "safety first" approach. In doing so we began by characterizing the effects of octreotide on counter-regulatory hormones to ensure that the broad inhibitory effects of octreotide on brain and gut hormones was not associated with blunting of the body's natural responses to the dangers of hypoglycaemia. We demonstrated the safety of octreotide in these terms in healthy volunteers and subsequently in diabetic patients [96,111,120,148]. Our work on glucose profiling targeted the effects of octreotide following pre-meal administration and particularly the effects of bedtime administration on overnight glucose and hormonal levels [105,109,150,151]. Adolescents with type I diabetes are known to experience a decrease in insulin sensitivity, which is thought to be linked in part to elevated circulating GH or IGF-I, particularly at night [178,179,180]. The GH inhibiting effects of octreotide enabled us to investigate this phenomenon more fully, while further characterizing the impact of octreotide on glucose profiles and counter-regulatory hormones. With Aarsen and Bruining et al we found that overnight 3-hydroxybutyrate levels were lower following octreotide therapy (50 µg single dose sc), indicating that hepatic ketogenesis was suppressed [103]. This finding and other supportive evidence by Scheen and colleagues [109] intrigued us as it indicated to us that octreotide might play a protective effect against the build-up of ketone bodies during periods of metabolic stress, e.g. during incipient ketosis. Since then some groups have studied octreotide in the setting of the treatment of overt diabetic ketoacidosis, and while octreotide is not an alternative to standard therapy, the addition of octreotide to regular therapy resulted in an improved profile of metabolic recovery from ketosis and hyperglycaemia [181,182]. Our work in teenagers with type I diabetes mellitus performed with Aarsen and Bruining et al bridged the gap between the anti-diabetic effects of octreotide (decreased glu-

cose levels, decreased GH levels) and its safety in terms of a relative lack of effect on glucagon, while decreasing hepatic ketogenesis [103].

Compared with our work on type I diabetes, the number of studies performed in type II diabetes was relatively small. Given the importance now ascribed to insulin resistance in overt type II diabetes mellitus and the much larger problem of metabolic syndrome, the effect of long-tem octreotide treatment on GH in insulin resistant states would be of significant interest today. The morbidity and mortality of diabetes is accounted for to a great extent by macro- and microvascular complications, and indeed diabetes mellitus is now recognized as being a primarily cardiovascular disease [172-175]. Uniting large and small vessels at a structural level is the endothelium, which, in contrast to the mid 1980's, is known to be sensitive to a vast number of pro- and anti-inflammatory signals. The aetiology of diabetic retinopathy, for instance, focuses on the interplay between various inflammatory and angiogenic mediators, such as, vascular endothelial growth factor (VEGF) and IGF-1 [183]. The findings of an early study in type I diabetic patients may be instructive for the future. In the study we performed with Kirkegaard's group we found that long term octreotide treatment (400 μg daily by continuous s.c. infusion for 1 year) was associated with a significant decrease in plasma LDL-cholesterol and serum apolipoprotein A-I, while von Willebrand factor and fibrinogen levels were reduced, but not significantly [184]. In a more recent study, Clemens et al also noted a decrease in endothelial dysfunction (assessed using serum thrombomodulin) in diabetic patients treated with 200 μg/day of octreotide for 6 months [185].

The utility of somatostatin analogues like octreotide in diabetic retinopathy is still an open question, with much preclinical evidence pointing to a role for somatostatin receptors in mediating new vessel growth. This anti-angiogenic effect may be mediated directly or indirectly via inhibition of IGF-1. In terms of the potential macrovascular effects of somatostatin analogues, work since the Clinical Development Program for octreotide has shown that large calibre vessels express somatostatin receptors (type 1 primarily) [186]. Modulation of angiogenesis by somatostatin analogues has been recognized since the work of E. Woltering and T. O'Dorisio [187]. The effect of long-term octreotide therapy on macrovascular complications in future studies of acromegaly may provide an indication as to whether effects of somatostatin analogues on the endothelium of diabetic patients could modulate accelerated atherosclerosis, and large-vessel pathology often seen in diabetes.

In conclusion, while the overall aim of the Clinical Development Program in diabetes mellitus did not conclude with an approved therapy for diabetes, the growing problem of type II diabetes indicates that long-term studies of the effect of octreotide on insulin resistance may be of interest. It is increasingly likely that the treatment of type II diabetes mellitus requires a multi-pronged approach in many patients to address metabolic abnormalities, such as, disordered insulin sensitivity, hepatic glucose output and hyperglycaemia. Given that these key components are all influenced by octreotide as outlined in this chapter, perhaps the utility of octreotide in this condition may have to be revisited in the future as an adjuvant or co-therapy. Microvascular diabetic retinal disease remains an area of active preclinical and clinical research with octreotide and other somatostatin analogues, and octreotide still may represent a viable pharmacotherapy for diabetic retinopathy and possibly a treatment for diabetic nephropathy that is refractory to ACE inhibitor therapy.

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Chapter IV.

The Clinical Development of Octreotide in Acromegaly

IV.I - CHARACTERISTICS OF ACROMEGALY

The physiological importance of hypothalamic somatostatin in the regulation of GH secretion by the anterior pituitary was demonstrated first in the early 1970's and was well characterised by the beginning of the 1980's. The clinical development team had gained an understanding of the effect of octreotide on GH and IGF-1 during the diabetes mellitus program (*see Chapter III*). Also, the pharmacological profile in animals and normal humans had shown us that octreotide could inhibit GH secretion potently without concomitant hypoglycaemia. Regarding acromegaly itself, it was understood that the disease was caused by excessive GH secretion from an anterior pituitary adenoma in the majority of cases[1]. Acromegaly due to ectopic GH releasing hormone (GHRH) or ectopic GH secretion was known to be rare[2,3,4]. GH hypersecretion was thought to be due to either an intrinsic loss of regulatory control by a population of anterior pituitary cells or due to excessive stimulation by the hypothalamus[5]. Subsequently, specific mutations in stimulatory G proteins (Gsα) have been identified that lead to unregulated expansion of a population of adenomatous cells secreting GH and other hormones[6,7,8]. This aetiology is similar to adenoma formation by many other glandular tissues.

From work by Alexander et al, it was acknowledged that acromegaly was a rare condition with a prevalence of 50-70 patients per million population[9], and this rate has not changed subsequently[10,11,12]. Acromegaly has an insidious onset and may be present for up to a decade before diagnosis[13]. During this time of unrecognised disease activity, organ damage can occur due to the effects of unopposed GH and IGF-1 hypersecretion (*Figure 17*). Therefore, the prognosis of acromegaly appears to depend on early detection and treatment, although prospective outcome data remains lacking even today. Mortality in acromegaly was known to be double that of the general population[14] and subsequent

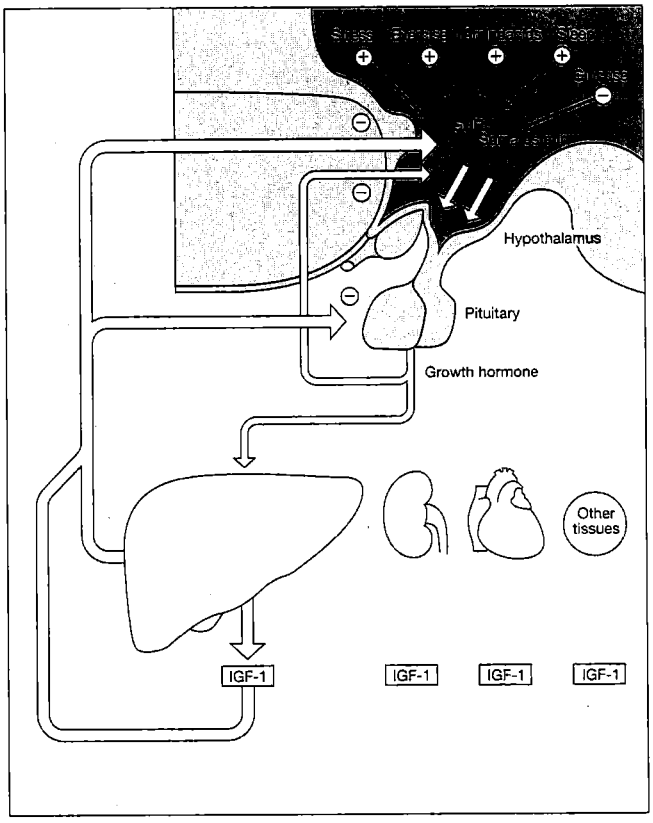

Figure 17. The stimulatory effect of growth hormone releasing hormone (GHRH) on pituitary growth hormone (GH) secretion is modulated by insulin-like growth factor I (IGF-I), a peptide formed in the liver and peripheral tissues under the influence of GH. IGF-I is thus involved in the negative feedback loop governing GH secretion. GH secretion is stimulated by ghrelin, stress, exercise and protein and inhibited by glucose. Dark lines, peripheral to central regulation; open lines, central regulation; light lines, putative regulation. (Adapted from Harris AG, Acromegaly, Lippincott Raven, New York, 1996).

evidence has shown that this rate can be as high as four times normal[15]. Wright et al reported that 26% of deaths occurred before the age of 50 years and 64% by the age of 60. Cardiovascular and respiratory disease and cancer cause the majority of deaths. Rajasoorya et al noted that patient survival in acromegaly was a function of GH level, with a higher mortality being noted in patients with higher post-treatment GH concentrations[16]. Impact on mortality appears only to be gained when GH levels post-treatment are below 2 μg/L. Bates et al noted similar findings; patients with GH levels of <5 μg/L had twice the normal mortality rate, while in patients with a nadir GH of <2.5 μg/L, mortality was only 1.4 times normal[17]. Taken together these data point to the necessity for tight GH control in the long-term management of patients suffering from acromegaly.

IV.II - TREATMENT OF ACROMEGALY IN THE PRE-OCTREOTIDE ERA

The standard therapy for acromegaly before and since the development of octreotide is transsphenoidal surgical resection[18]. This surgical approach introduced by H. Cushing, has been used for nearly a century, but success rates vary according to the ease of resection, tumour size/bulk and surgical expertise. Data available at the time of the clinical development program suggested that 60-80% of patients with GH-secreting microadenomas (<10mm diameter) achieved a cure following surgery. However, this dropped to 20% for macroadenomas[19]. A further complication was the variable definition of 'cure'. Historically, many surgical series chose a GH level of ≤ 10 μg/L or ≤ 5 μg/L after an oral glucose tolerance test (OGTT) as normal. In the 1980's it was realised that the definition of 'normal' GH had to be revised downwards to < 2 μg/L or less after OGTT, as active disease could be detected via IGF-1 at higher GH concentrations. We incorporated this advance into the clinical development program for octreotide in acromegaly by performing[12] and 24 hour GH profiles in which 75 % of GH values had to be < 2 μg/L before we considered disease to be quiescent. Patients in whom pituitary surgery was unsuccessful (or too dangerous) had two options before the advent of octreotide, radiotherapy and dopamine agonists. Pituitary radiotherapy has the disadvantages of having a slow onset of action and variable efficacy. Only 50% of patients were known to have 'normal' GH (≤5 μg/L) a decade post radiotherapy. Also radiotherapy damages surrounding normal pituitary tissue, causing hypopituitarism and concerns still exist regarding the incidence of second brain tumours [20,21]. Before the development of octreotide the only medical therapy for acromegaly was treatment with dopamine agonists like bromocriptine. In normal individuals, L-dopa increases GH secretion, but in acromegaly a paradoxical decrease had been reported. Also, some pituitary adenomas derive from GH and prolactin co-secreting cells and suppression of both hormones with dopamine agonists can be achieved. However, the biochemical efficacy of these agents is variable, with only 10-20% of patients achieving normal GH and IGF-1 concentrations[22].

IV.III - THE CLINICAL DEVELOPMENT PROGRAM

IV.III.I - Introduction

When developing a drug for the treatment of a specific condition, one must be able to demonstrate an unmet need for the new therapy to address. In the case of octreotide in acromegaly, surgical, radiotherapeutic and medical treatments were all available at the time of the clinical development of octreotide. We identified that patients were not achieving adequate biochemical control in terms of GH and IGF-1 normalisation with any of the available treatments [23,24,25]. Also, significant treatment failure occurred with both surgery and dopamine agonists, while radiotherapy often required many years for GH control to manifest itself. Furthermore, risks of general anaesthetic and pituitary surgery meant that elderly or debilitated patients were often unsuitable for first-line therapy. The research program in acromegaly was designed to address each of these unmet needs and define a specific role for octreotide.

The phase I and II trials with octreotide had demonstrated potent selective inhibition of GH and a good safety profile in terms of glucose metabolism[26]. As acromegaly is a relatively pure model of the effects of GH and IGF-1 excess, our pharmacological data regarding GH suppression in healthy volunteers provided us with a clear rationale for using octreotide to improve hormonal and clinical disease measures in acromegaly. We designed and pursued studies to document rapidly the efficacy and safety in acromegalic patients. Octreotide was distributed to clinicians initially on a compassionate use basis in acromegaly and gut endocrine tumours. The benefits reported by acromegalic patients and their physicians stimulated us to collect data retrospectively in the form of a case collection. These data were collected in a standardised fashion (outlined below) to allow us to compare and judge treatment effects across a widely scattered population. Standardisation of data collection was a key factor due to the specific challenges of treating a rare condition like acromegaly. By definition, the clinical development program had to be multinational and cooperative in order to recruit sufficient patient numbers to perform pharmacological and comparative clinical studies. Cohesion amongst clinical research groups in various countries was crucial to the eventual success of the clinical development program for octreotide in acromegaly, and this represented one of our primary research functions. As the retrospective case collection was being performed and analysed, we instituted a series of prospective studies that examined safety, signs and symptoms of disease and compared octreotide with available therapy. These studies were performed to satisfy some of the requirements of drug regulatory authorities that sought placebo-controlled efficacy and safety data.

IV.III.II - Pituitary Pharmacodynamics of Octreotide

Pharmacological data from normal volunteers demonstrated that octreotide had profound effects on static and dynamic pituitary function tests[24]. Exercise-induced GH secretion was significantly reduced by iv octreotide.

Subcutaneous octreotide (50 and 100 μg) reduced thyrotropin releasing hormone (TRH) induced rises in thyroid stimulating hormone (TSH) and prolactin. Combined pituitary function testing with TRH, gonadotropin releasing hormone (GnRH) and insulin was also performed in healthy subjects. TRH-stimulated prolactin and TSH concentrations fell during octreotide infusion. Intravenous octreotide blunted the rise in GH due to insulin-induced hypoglycaemia, although no effect on ACTH or cortisol response was seen. Lutenising hormone (LH) dropped slightly with octreotide but FSH and posterior pituitary hormones were unaffected.

We investigated the pharmacology of octreotide in acromegaly[24]. Pharmacokinetic studies in 12 acromegalic patients following single 100 μg iv or sc. doses of octreotide showed that the disposition and elimination half-lives and the absolute bioavailability were comparable to healthy volunteers. The mean t_{max} following sc octreotide was 44 ± 16 minutes in acromegalics and 23 ± 7 minutes in healthy volunteers ($p<0.01$), while the mean AUC was 490 ± 185 ng/mL/min in acromegalics and 676 ± 159 ng/mL/min in volunteers ($p<0.05$).

IV.III.III - Clinical Research with Octreotide in Acromegaly

Data on the clinical effects of octreotide in acromegaly were retrieved in two ways, retrospectively and prospectively. The retrospective data was collected from 155 individual patients treated with octreotide on a compassionate need basis between 1983 and 1987. Sandoz provided octreotide at an early stage to experienced endocrinologists for the treatment of new patients or others that had failed or were unsuitable or unwilling to undergo existing standard therapies. The following recommendations were provided to facilitate data collection and standardisation:

1. Dose titration should begin with 50 μg sc octreotide twice or three times daily. Based on early clinical findings from Lamberts and colleagues, the eventual optimal s.c. dose was found to be 100 μg eight hourly, as GH suppressive effects only lasted for four to six hours after 50 μg octreotide.
2. Maximum daily dose was 300 μg per day sc, but this could be exceeded if a clinical response was reasonably expected, and tolerability was satisfactory. The highest daily dose achieved was 1500 μg[27].
3. Adverse event profiles were to be monitored extremely rigorously. We modelled our adverse event monitoring on the possible side effects that could be expected from somatostatin and octreotide's biological effects (gut hormone inhibition, malabsorption, gallstones, glucose intolerance). In the case of biliary stones, ultrasonography pre- and post treatment was recommended where feasible.

Efficacy data was measured, collected and reviewed under the following headings:

1. Improvement in signs and symptoms
2. Magnitude of reduction in GH and IGF-1 concentrations
3. Reduction in GH and IGF-1 compared with bromocriptine
4. Effect on pituitary tumour size
5. Clinical response in terms of associated safety/tolerability issues

Sandoz personnel performed collection of data and interactions with clinician investigators, with multiple on-site visits and discussions. Case report forms were designed to capture standardised demographic information, disease characteristics and history, radiology data, disease response and adverse events (*Table 6*). Octreotide was provided to the investigators on the understanding that case report forms would be completed at the onset on treatment and on a monthly basis thereafter. Data were collated and analysed centrally by the clinical development team.

The patient population was heterogeneous in order to maximise the number of patients receiving octreotide, but also to determine effects in treatment-naïve patients (who were unwilling or unable to undergo standard therapy) and in those who had undergone failed surgical, medical or radiological therapy. The inclusion criteria were simple, with demonstration of acromegaly by elevated basal GH (>5 μg/L), or a failure to suppress GH secretion to <2 μg/L following a 75-100 g OGTT, or an elevated IGF-1 level.

Data from the compassionate use program were assessed retrospectively. A total of 155 patients from 20 centres in Europe, Canada, Australia and New Zealand were included. The retrospective analysis was accompanied by two small prospective trials performed from September 1986 to February 1987 involving 23 patients. Data collection in the prospective trials was similar to that for the retrospective analysis. The decision to pursue prospective trials was taken because of the evolution of good clinical practice (GCP) guidelines and regulatory oversight by the EU (then the EEC) to match the FDA guidelines in force in the United States. Regulatory approval for the use of octreotide in acromegaly in several European and a number of other countries was based on the combined results of the retrospective case collection and the two small prospective trials. The final number of patients analysed was 178, who were treated with doses of octreotide that ranged from 50-1500 μg/day administered mainly by subcutaneous injection or by continuous subcutaneous infusion in a limited number of patients. Of particular note was the fact that 135 patients had previously failed to respond to (or were unsuitable or unwilling for) surgery, radiotherapy, bromocriptine or combinations of these treatments. This large subgroup was representative of the unmet needs of acromegalic patients up to the advent of octreotide.

Due to the heterogeneity of the patient population and the multicentre design, octreotide treatment was not entirely standardised and not all patients were assessed for all clinical parameters. The safety population was 178 patients and of these 149 were evaluable for efficacy in reducing GH and 175 were evaluated for other efficacy parameters. The mean duration of therapy was 226 days, with some patients receiving octreotide for up to 35.4 months at the time of analy-

Table 6: Case report form used for data collection in acromegaly during the Clinical Development Program.

Case Report Form Heading	Data Collected
Background Information	Demographic data, age, weight, height, sex, race and background medical history. History and treatment of acromegaly.
Coexistent Diseases and Conditions	Significant medical conditions present at baseline.
Prior Medication	Drugs taken in the three months prior to baseline.
Concomitant Medications	Any other medications taken during treatment with octreotide.
Physical Examination	Findings of complete physical examination were entered at baseline and every subsequent visit.
Vital Signs	Standing and supine heart rate and blood pressure in addition to temperature.
Clinical Evaluation	Patients disease sign and symptom severity was rated by the investigator at baseline and on each subsequent visit as: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. Signs and symptoms evaluated were: distortion of facial features, acral growth, soft tissue swelling, peripheral neuropathy, carpal tunnel syndrome, paresthesiae, osteoarthritis, myopathy, headache, impairment of vitality, somnolence, depression, hyperhydrosis/sweating, hypertrichosis, decreased libido, erectile dysfunction, dyspnoea, sleep apnoea, galactorrhoea, other endocrine disturbances and visual impairment. Endocrine and neurological examinations were performed specifically, and finger circumference was measured by graded rings on the 4th finger of each hand.
Electrocardiographic Evaluation	A 12-lead electrocardiogram was recorded at baseline and during study visits.
Opthalmological Testing	Visual fields and perimetry were measured by the Goldman and Friedman methods before and during treatment visits.
Computerised Tomography	Pituitary tumour dimensions, radiological characteristics and extension were recorded prior to treatment and copies of scans were to be held by Sandoz. A grading scheme was used for enclosed tumours (I = microadenoma (<10 mm), II = adenoma (>10 mm)) and invasive tumours (III = localised, IV = diffused). Suprasellar expansion was also graded according to severity as A, B or C. Pituitary tumour size changes were assessed as mm reductions in vertical, horizontal or anterior-posterior diameters.
Gallbladder Echography	A gallbladder and biliary tree ultrasound was performed prior to starting octreotide therapy and during treatment if so requested by investigator.
Chest X-ray	A chest radiograph performed within the previous six months was to be available before starting octreotide, and a follow up X-ray was performed during treatment.
Laboratory Evaluation	The following parameters were measured at baseline, during treatment and if early discontinuation of octreotide occurred: haemoglobin, haematocrit, erythrocyte, leukocyte and platelet counts (plus differential), ESR, prothrombin time, AST, ALT, alkaline phosphatase, g-GT, total bilirubin, urea, creatinine, uric acid, calcium, albumin, sodium, chloride, potassium, cholesterol, triglycerides. A urine dipstick for albumin, glucose, acetone, pH, erythrocytes and casts was recorded.
Plasma GH	Day curves for GH were to be determined before octreotide and at discretionary timepoints during treatment. Only similar day-curve timepoints were compared in subsequent statistical analyses.
IGF-1	IGF-1 was recorded before and during treatment
Diabetes evaluation	Insulin requirements and glycaemic control were measured in diabetic patients.
Oral Glucose Tolerance Test (OGTT)	A standard 75 g OGTT was performed following an overnight fast, and glucose, insulin and GH levels were measured. This was performed before octreotide commenced and during octreotide therapy.
Endocrine Assessment	Prolactin, TSH, T3 and T4 were measured at baseline and during treatment.
Dynamic Pituitary Function Testing	TRH, GnRH, GHRH and insulin tolerance tests were optional.
Drug Administration Record	Drug dose, timing of injections and dose escalations were all recorded. The actual time of administration of octreotide during GH day curves/profiles was to be recorded to assess the onset and degree of GH suppression.
Adverse Events	Patients were questioned specifically regarding any adverse events that occurred during octreotide treatment. The nature, severity, duration and relationship of the adverse event to octreotide were recorded by the investigator.
Interim Evaluation	All interim response and adverse event data were recorded on separate forms.
Final Evaluation	This form detailed the whether the patient completed the scheduled course of octreotide and any reasons for early termination.

sis. Overall results showed that octreotide administration significantly reduced GH in most patients and similarly most individuals experienced a rapid improvement in clinical symptoms (*Table 7*). Pituitary tumour shrinkage by more than 20% occurred in 19 out of 31 evaluable patients after octreotide therapy. Octreotide was well tolerated up to a high daily dose (1500 µg/day) and adverse events were experienced in 62/178 (34.4%) patients. Over 90% of these adverse events were rated as being only mild to moderate in severity and most consisted of transitory gastrointestinal upset (abdominal discomfort, nausea, flatulence and loose stools). Only one patient discontinued octreotide therapy due to an adverse event (diarrhoea). Octreotide had only a marginal effect on glucose tolerance. Laboratory data including thyroid function did not vary in a clinically relevant manner with octreotide therapy. One finding of note was the discovery of non-symptomatic gallstones in three patients. As native somatostatin inhibited gallbladder contraction, concerns were expressed that prolonged octreotide therapy could lead to the development of gallstones. For this reason we became highly vigilant regarding gallbladder function in all of our subsequent prospective trials. Moreover, the decision was made to actively foster study of this phenomenon (*see Chapter VII*).

The results of the retrospective and prospective studies were combined with data from a further 11 patients in the U.S. and published later in 1991 [28]. Analysis of this final collection showed a clinical response rate of 88%, with lowered GH levels in 172/182 evaluable patients (*Table 8*). Of these respon-

Results (% improved; total improved/total assessed)	
Distorted facial features:	45.2 % (76/168)
Headache:	84 % (79/94)
Ring Size:	55 % (22/50)
Impaired vitality:	78.6% (77/98)
Paresthesia:	87.3 % (83/95)
Carpal Tunnel Syndrome:	70.9 % (56/79)
Osteoarthritis:	58.2 % (46/79)
Somnolence:	64.9 % (37/57)
Myopathy:	71.9 % (41/57)
Peripheral Neuropathy:	71.9 % (41/57)
Decreased Libido:	48.0 % (24/50)
Depression:	68.0 % (32/47)
Hypertrichosis	23.0 % (11/47)
Erectile Dysfunction:	51.7 % (15/29)
Dyspnoea:	47.0 % (8/17)
Galactorrhoea:	66.6 % (10/15)
Sleep Apnoea:	33.3 % (1/3)

Table 7: Improvement in signs and symptoms with octreotide therapy in 178 patients with acromegaly case collection group

Dosage, µg/d	Total # Patients	Before Octreotide Therapy	After Octreotide Therapy	P
		GH, µg/L		
100	30	38.2 ± 5.8 (27.7)	21.1 ± 4.7 (9.2)	.0001
150	16	30.7 ± 6.8 (18.7)	12.1 ± 4.6 (3.9)	.0001
200	23	41.9 ± 11.6 (19.1)	16.1 ± 5.4 (6.4)	.0001
300	69	38.2 ± 8.8 (16.2)	9.3 ± 2.1 (4.4)	.0001
400	11	41.2 ± 16.6 (24.8)	5.1 ± 1.1 (4.4)	.0001
500	4	49.9 ± 19.7 (45.4)	12.4 ± 3.4 (11.4)	..0001
600	13	47.2 ± 17.0 (24.6)	9.8 ± 3.8 (4.8)	.0002
750	3	7.6 ± 1.3 (7.2)	3.8 ± 0.7 (3.4)	.002
1500	8	65.9 ± 30.0 (16.3)	13.4 ± 8.4 (6.7)	.0003
All doses	**182**	**39.4 ± 4.4**	**12.2 ± 1.5**	**.0001**
		IGF-1, U/mL		
100	24	4.00 ±0.61 (2.96)	2.38 ± 0.37 (1.86)	.0001
150	10	7.69 ± 2.41 (5.52)	3.90 ± 1.25 (2.30)	.02
200	11	4.67 ± 0.79 (3.90)	2.01 ± 0.29 (2.10)	.003
300	38	5.63 ± 0.46 (5.15)	2.74 ± 0.27 (2.40)	.0001
400	2	11.50 ± 5.90 (11.50)	2.14 ± 0.67 (2.14)	.0001
500	3	7.89 ± 2.36 (7.80)	3.07 ± 0.23 (3.60)	.0001
600	3	7.88 ± 2.36 (7.80)	3.60 ± 0.23 (3.60)	.002
750	2	3.35 ± 0.05 (3.35)	1.21 ± 0.30 (1.21)	.002
1500	5	4.72 ± 0.84 (4.30)	1.94 ± 0.37 (1.91)	.02
All doses	**99**	**5.62 ± 0.41**	**2.64 ± 0.19**	**.0001**

Table 8. Mean (±SE) serum GH and IGF-1 concentrations before and at final evaluation of octreotide therapy in 189 acromegalic patients. P values refer to comparison with pretreatment values. The number of patients for all doses for GH includes five patients who received a total dosage other than those listed; The number of patients under the heading IGF-1 includes one patient who received a total dosage other than those listed. (Adapted from Vance ML and Harris AG [28])

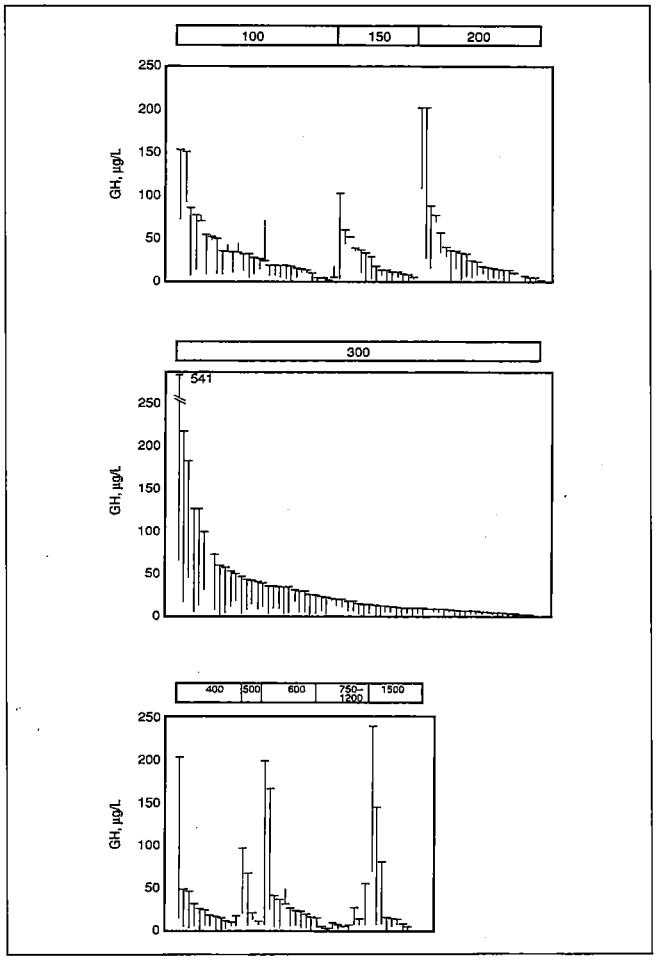

Figure 18. Serum growth hormone (GH) before and at final evaluation of octreotide therapy in a subset of 99 evaluable acromegalic patients. Each vertical line represents one patient; the horizontal line indicates the pretreatment value. Patients are grouped according to total octreotide dosage (in micrograms per day) at final evaluation, shown at the top of the figure. (Adapted from Vance ML and Harris AG[28]).

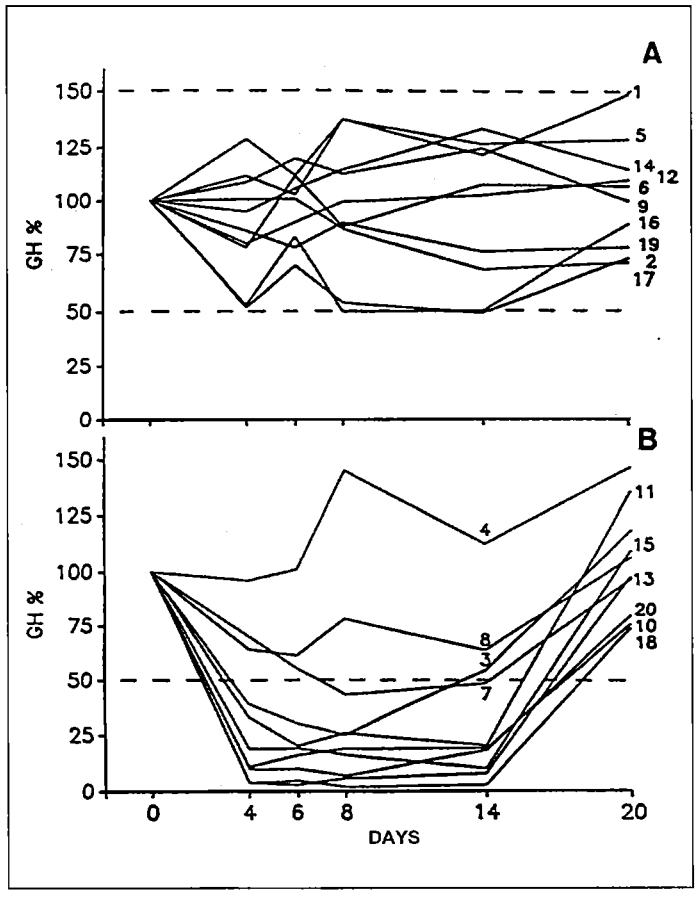

Figure 19. Individual mean plasma GH levels in samples taken hourly from 0700-1800 h as a percentage of pre-treatment levels (day 0) during treatment (days 4, 6, 8, and 14) and 6 days after treatment (day 20) with octreotide (up to 200 µg daily) or placebo for 14-days in 20 patients with acromegaly. Patient numbers are indicated in the figure.
A: Treated with placebo; the dashed lines indicate approximations of the spontaneous variation of plasma GH.
B: Treated with octreotide; the dashed line indicates reduction of GH levels by 50%. (Adapted from Fredstorp L, Harris A, Haas G, Werner S[30]).

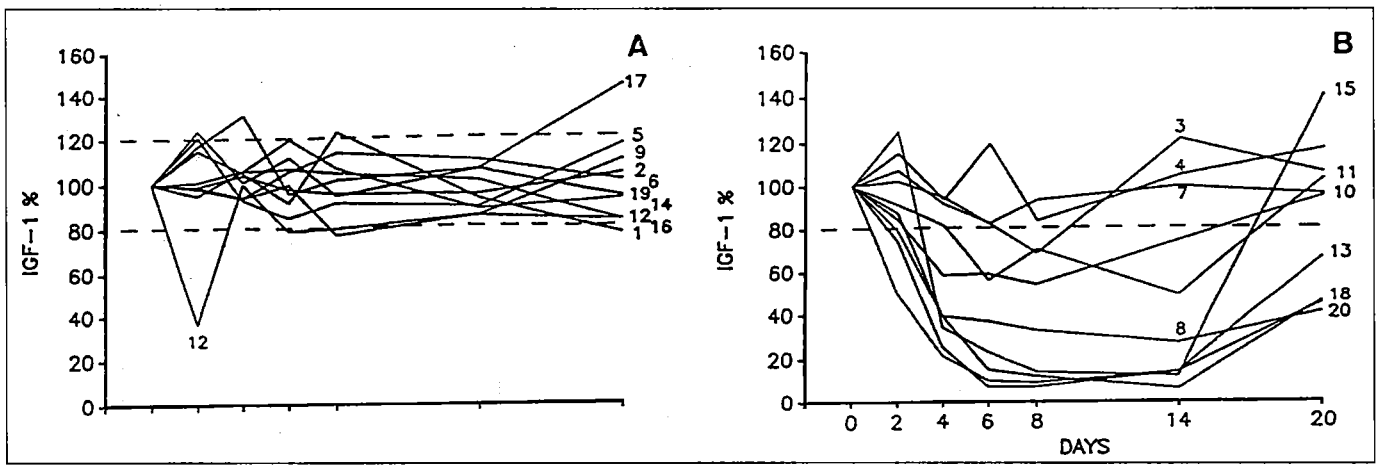

Figure 20. Individual serum IGF-I levels in fasting samples of 0700 h as a percentage of pre-treatment levels (day 0) during treatment (days 2, 4, 6, 8 and 14) and 6 days after treatment (day 20) with octreotide (up to 200 µg daily) or placebo for 14-days in 20 patients with acromegaly. Patient numbers are indicated.
A: treated with placebo; the dashed lines indicate approximations of the spontaneous variation of serum IGF-1.
B: treated with octreotide; the dashed line indicates reduction of IGF-I levels by 20%. (Adapted from Fredstorp L, Harris A, Haas G, Werner S[30]).

ders, 82/182 had GH <5 μg/L (*Figure 18*). Mean IGF-1 levels pre- and post- treatment were 5.62 ± 0.41 IU/mL and 2.64 ± 0.19 IU/mL, respectively (normal <2.2 IU/mL). Fifteen of 34 radiologically evaluable patients experienced a >20 % decrease in pituitary tumour size during treatment. The side effect profile was similar to the 178 patient collection.

While the collection of data was ongoing at Sandoz, other groups had already published prominently in the medical literature regarding short-term octreotide therapy in acromegaly. My colleague from Sandoz E. del Pozo with S. Lamberts reported that 50 - 100μg of octreotide decreased GH levels by up to 86% over a period of 2 - 6 hours following subcutaneous (sc) administration[29]. The 50 μg dose suppressed GH by 62% of pre-treatment levels, while the 100 μg dose suppressed GH by 81% and for a longer duration. These short-term effects were studied and confirmed prospectively by us in the first double-blind placebo-controlled trial of octreotide in acromegaly at the Karolinska Institute in Sweden (*Figure 19, 20*)[30]. We performed a prospective multicentre dose-ranging study of octreotide in France over six months with G. Sassolas et al.[31]. Fifty-eight acromegalic patients were included and received increasing doses (300-1500 μg) of octreotide. Of these, 34 were maintained on octreotide for 12-26 months on a minimal efficacious dose. GH normalised in 22% of the patients, improved in 56%, and remained unchanged in 22% regardless of the dose. This study confirmed that the optimal dose was 100 μg eight hourly in 50% of the patients, but 20% required a total daily dose of 1500 μg. Pituitary tumour size reduction occurred in 47% of the patients harbouring large tumours (*Figures 21, 22*).

Chronic octreotide treatment of acromegaly was reported in the mid-1980s and demonstrated maintenance of short-term benefits[32], with further decreases in GH being reported over time[33]. Accompanying the inhibition of GH secretion, circulating IGF-1 levels also decreased in long-term studies and normalised in up to 50% of patients. This high response rate was quite uniform across these long-term studies and the Sandoz data collections, quite in contrast to the variable responses seen with dopamine agonists and surgery. In order to classify patients better, we performed a study to assess the long-term responsiveness of acromegaly. In this study, with K. Schmidt et al, we found that patients' responses to acute administration of octreotide doses in acromegaly predicted whether or not they would respond adequately to long-term treatment[34].

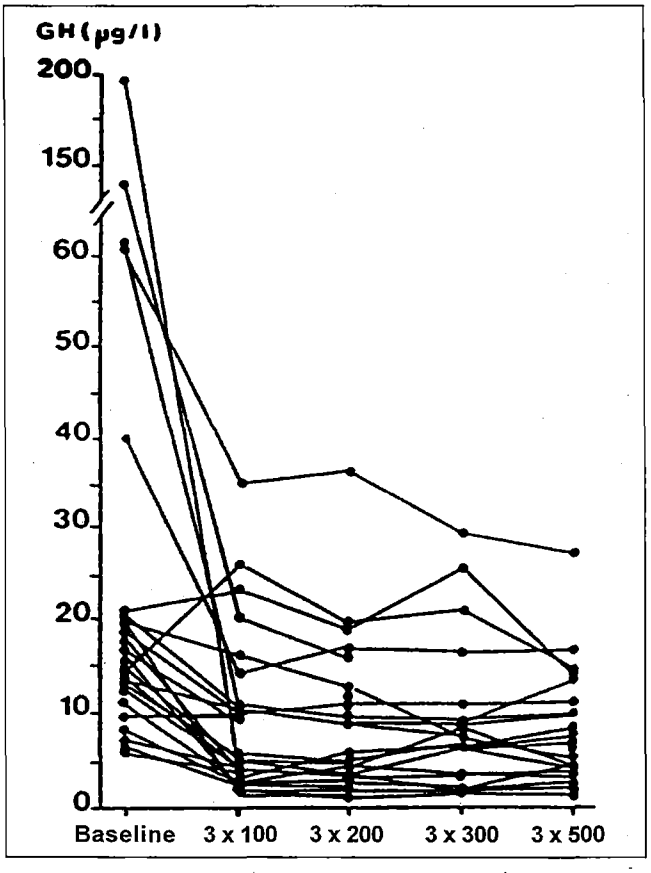

Figure 21. Individual mean plasma GH concentrations in 29 patients with acromegaly treated with high-dose octreotide (1500-μg/day). Each line represents an indicidual patient and their respective GH concentrations (vertical axis) during incremental rises in octreotide dose (horizontal axis). The numbers on the horizontal axis refer to daily dose of octreotide. (Adapted from Sassolas G, Harris AG, James-Deidier A [31]).

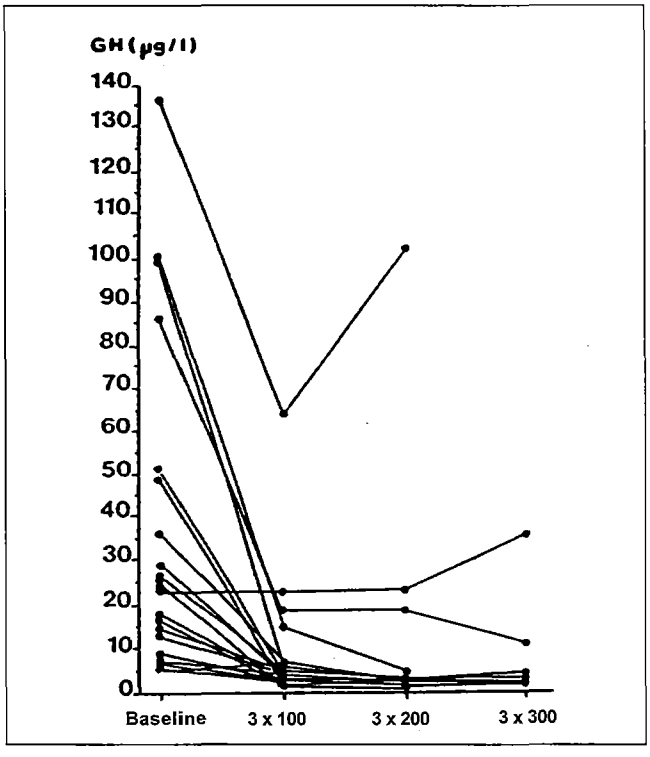

Figure 22. Individual mean plasma GH concentrations in 27 acromegalic patients who did not reach the maximum 1500 μg daily octreotide dose during dose escalation. When responders (normalised and improved) were considered, the lowest dose was optimal in 50%, whereas the maximal dose was the most efficient in 20% however, the difference in plasma GH reduction was often minimal (2 μg/L in mean GH levels. The numbers on the horizontal axis refer to the daily dose of octreotide. (Adapted from Sassolas G, Harris AG, James-Deidier A [31]).

At the time of the Clinical Development Program bromocriptine occupied the leading position for medical treatment in acromegaly, and as such, represented a major obstacle to the acceptance of octreotide. Clarification of the relative benefits of octreotide and bromocriptine in acromegaly was important for the success of our clinical development program. We performed a number of studies with octreotide and bromocriptine to investigate the relative efficacies of the two treatments. In conjunction with the Department of Internal Medicine, Erasmus Medical Centre, Rotterdam, we studied the acute effects of octreotide and bromocriptine alone and in combination in acromegaly[35] (*Figure 23*). These findings were confirmed by a similar study we conducted in Norway with J. Halse et al[36]. These studies followed on from early direct comparisons that demonstrated better GH suppression with octreotide than bromocriptine [37,38]. We found that octreotide suppressed GH secretion more markedly than bromocriptine and had a faster onset of action (*Table 9*). Most interestingly, we reported that the two drugs, given in combination, provided better control of GH than either one alone, although this effect was not seen by another group[39]. Others have also reported the increased GH suppressive effect of combination therapy[40]. The benefit of co-administration is partially explained by the fact that octreotide increases the bioavailability of bromocriptine by approximately 40%, while the pharmacology of octreotide is unaffected[40].

Leading on from this comparative work, we performed an analysis with van der Lely at the Department of Internal Medicine, Erasmus Medical Centre, Rotterdam, of the effects of age and sex on the sensitivity of GH secretion to octreotide and bromocriptine[41]. This study of 100 acromegalic patients found that tumour size correlated well with basal and 24-hour mean GH secretion. Also baseline and mean 24 hour GH were closely correlated. Interesting there was only a correlation between GH and IGF-1 levels only up to a certain GH concentration (not above 40 µg/L). This indicated the presence of an upper threshold for GH stimulation of maximal IGF-1 production, above which no further enhancement of IGF-1 secretion occurs. There was a negative relationship between age and circulating GH or IGF-1 in male patients, but none between tumour volume and age (*Figures 24, 25*). Higher circulating prolactin predicted better subsequent GH suppression with bromocrip-

	Octreotide	Bromocriptine
Mean GH day profile (µg/L)		
Baseline	13.8 ± 5.2	18.8 ± 7.5
Day 14	4.0 ± 1.4[a]	7.3 ± 1.9[a]
Day 28	3.3 ± 1.0[a]	5.3 ± 1.2 a[b]
Day 56	2.9 ± 0.7[a]	5.4 ± 1.2 a,[b]
Follow-up	12.5 ± 4.4	13.8 ± 4.4
Mean IGF-1 (U/mL)		
Baseline	3.0 ± 0.36	2.93 ± 0.40
Day 14	1.60 ± 0.43[a]	2.30 ± 0.31[a]
Day 28	1.43 ± 0.36[a]	2.04 ± 0.31[a]
Day 56	1.43 ± 0.36[a]	2.13 ± 0.27[a,c]
Follow-up	2.90 ± 9.38	3.09 ± 0.33

Table 9. Effects of treatment with either octreotide 50 µg s.c. or bromocriptine 2.5 mg on serum GH and IGF-1 concentrations in 25 patients with acromegaly. Results obtained on days 14, 28, 55, and 56 represent treatment effects. Data are presented as the mean ±SEM.
a Significantly different from baseline ($P < 0.01$).
b Significantly different from day 14 of treatment ($P < 0.01$).
c One patient taking 15 mg bromocriptine daily since day 37 was included in the analysis.
(Adapted from Wagenaar AH, Harris AG, van der Lely AJ, Lamberts SWJ[35]).

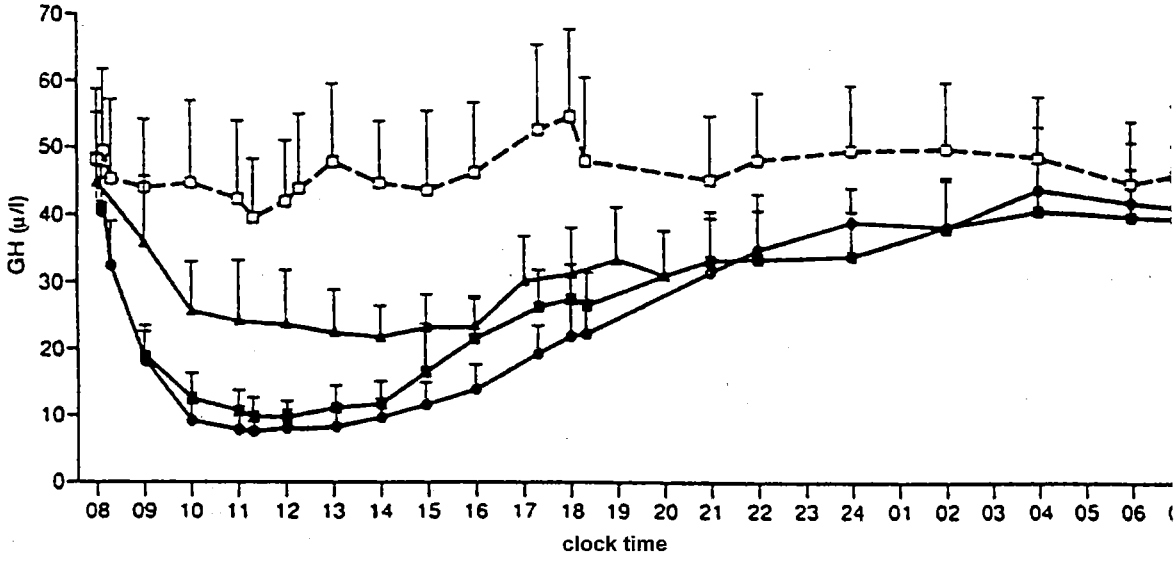

Figure 23. Absolute mean changes of circulating GH levels throughout the day in 25 acromegalic patients treated with placebo (n = 51), octreotide (50 µg sc) (n = 51), bromocriptine (2.5mg po) (n = 40) or combination therapy (n = 25). ❑ = placebo; ▲ = bromocriptine; ■ = octreotide; ● = octreotide and bromocriptine. (Adapted from Wagenaar AH, Harris AG, van der Lely AJ, Lamberts SWJ[33]).

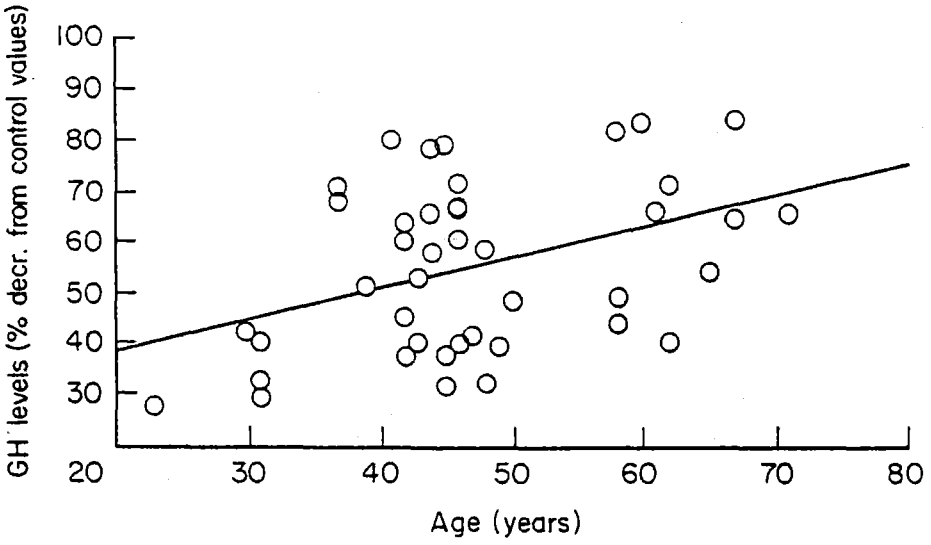

Figure 24. Correlation between age and the decrease in GH levels after 50 µg octreotide subcutaneously in 42 male acromegalics. The decrease in GH level reflects the area under the curve of the first 12 hours after octreotide administration as percentage of the curve on the control day. r =0.32; P = 0.014. (Adapted from van der Lely, Harris AG, Lamberts SWJ[41]).

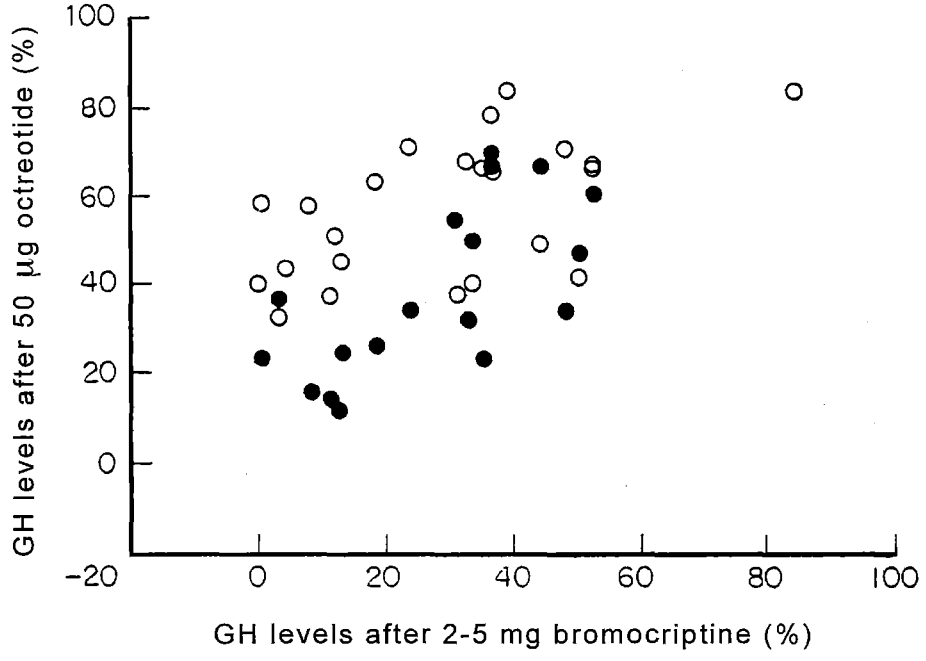

Figure 25. Correlation between decrease of GH levels after octreotide and bromocriptine. The decrease in GH level reflects the area under the curve of the first 12 hours after the administration of each of the drugs as percentage of the area under the curve on a control day. Both decreases correlate well: r = 0.60. P<0.01. Note that men (○, n = 23) show a greater decrease in GH levels after octreotide, while women (●; n = 18) tend to show a greater decrease after bromocriptine. r = 0.60; P < 0.01. (Adapted from van der Lely, Harris AG, Lamberts SWJ[41]).

tine. Elderly and male patients responded most profoundly to octreotide, and acromegaly tended to be less active in older patients. Consequently it was felt that these elderly patients could benefit from octreotide as first-line medical therapy, rather than resorting to pituitary surgery with all of its attendant risks. Recently in 2002, Colao et al confirmed that elderly patients with acromegaly had lower GH and IGF-1 levels, and that a negative correlation existed between patients' age and GH and IGF-1 levels[42]. However unlike in our study this group did find a negative correlation between patients' age and tumour size. Taken together these results suggest that elderly patients with acromegaly have less active disease and possibly smaller pituitary adenomas.

IV.III.IV - Formulations of Octreotide

Despite the marked benefits of octreotide on disease severity, we recognised the compliance problems associated with administering octreotide by two or three daily injections. We also sought to reduce disease activity further with alternate administration forms that exhibited greater 24-hour GH suppression. Continuous subcutaneous insulin infusion pumps had been developed for use in patients with type I diabetes mellitus. We adapted this technology for use with octreotide in acromegaly. It had been noted in previous injection studies that GH escape could occur approximately four to six hours after octreotide administration. The aim of sc. infusion administration of octreotide was to provide consistent GH suppression via sustained plasma octreotide levels. In 1987 we reported with Christensen from Orskov's group and Timsit et al that sc. pump-administered octreotide provided superior and stable GH suppression in short-term studies [43,44] (*Figures 26, 27*). We confirmed these results with Tauber et al., the following year with long-term sc. pump octreotide therapy[45]. We subsequently demonstrated with Roelfsema and colleagues that continuous sc. octreotide at a dose of 300 - 400 µg/24 hr reduced IGF-1 to a significantly greater degree than intermittent injections[46]. However, James et al found no difference between intermittent injections and continuous sc. infusion of octreotide in terms of IGF-1 control, but reported better subjective symptom improvement and less glucose intolerance with pump delivery of octreotide[47].

Continuous pump infusion of octreotide heralded the development of repeatable depot octreotide in the 1990's, which confirmed the importance of consistent 24-hour GH and IGF-1 control. A major concern with both delivery formulations was the possibility of increased adverse events. When trials of continuous sc. pump octreotide were reviewed, no rises in glycaemic or biliary side effects were seen[48]. With respect to gallstone formation specifically, we found that no increased risk exists with continuous sc. infusion of octreotide[49]. Although the long-acting repeatable (LAR) and intermittent sc formulations of octreotide are the predominant routes of delivery and patients found the pump form convenient and effective. Moreover, the experienced gained with pump delivery facilitated the development of the depot long acting repeatable (LAR) form of octreotide.

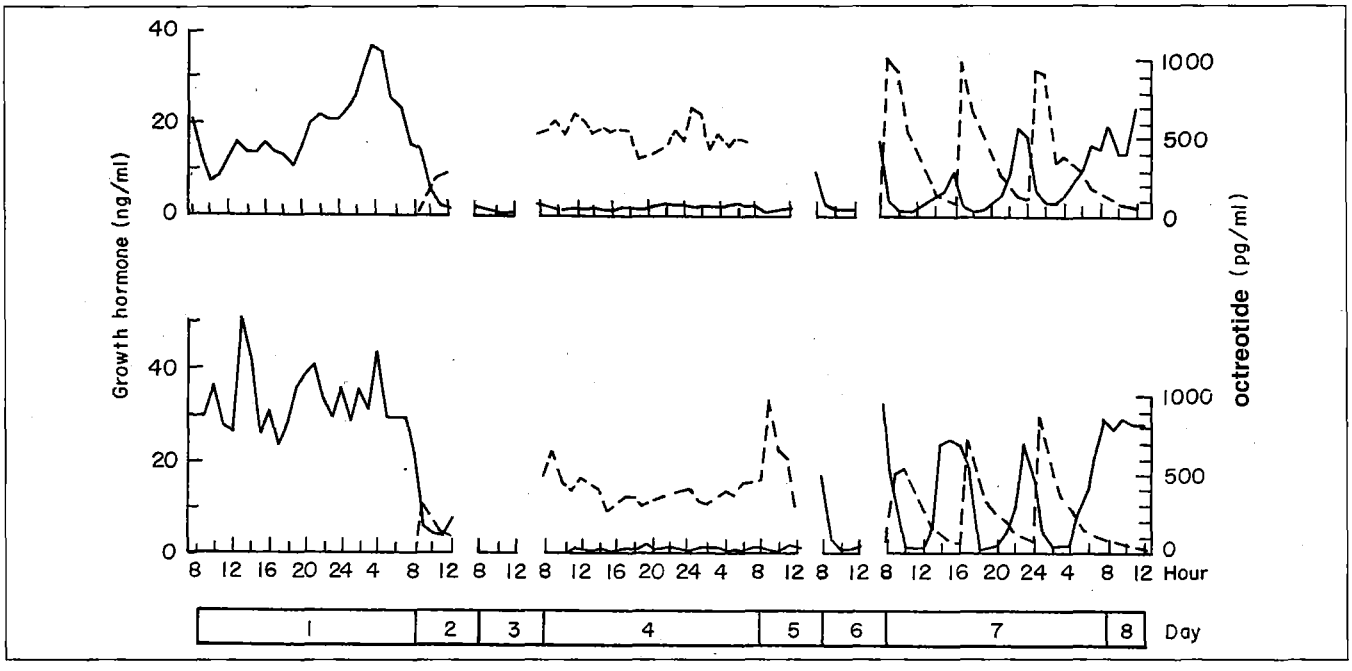

Figure 26. Serum growth hormone (GH) and octreotide profiles in two patients treated with a continuous subcutaneous infusion of octreotide. GH concentrations are shown on the vertical axis (left), while octreotide concentrations are on the vertical axis on the right. The horizontal axis displays time in hours and days. GH control with octreotide was achieved across the full 24-hour period during sc infusion, while three times daily sc injections of octreotide (day 7, right) showed octreotide and GH levels fluctuating reciprocally. (-) Serum GH values; (---) serum octreotide values. (Adapted from Christensen SE, Weeke J, Orskov H, Moller N, Flyvbjerg A, Harris AG, Lund E, Jorgensen J [44]).

As peptides such as octreotide are rapidly degraded in the gut, an orally administered form was not felt to be feasible. However, clinically relevant effects (50 % reduction in GH) were achieved with 4–8 mg oral octreotide three times a day in acromegalic patients [50]. Although acceptable plasma octreotide levels have been achieved following oral administration [51], 24-hour octreotide concentrations were variable and not dose-dependent. A nasal insufflation formulation of octreotide was also developed, which demonstrated approximately 25% bioavailability via the nasal mucosa [52]. We showed that a 500 µg dose of nasally administered octreotide had the bioavailability of 100 µg of sc. injected octreotide, but was not as potent as the injectable form *(Figures 28, 29, Table 10)*. Neither oral nor nasal octreotide were developed commercially due to the relatively poor pharmacological profile compared with the sc injectable and infusion pump formulations.

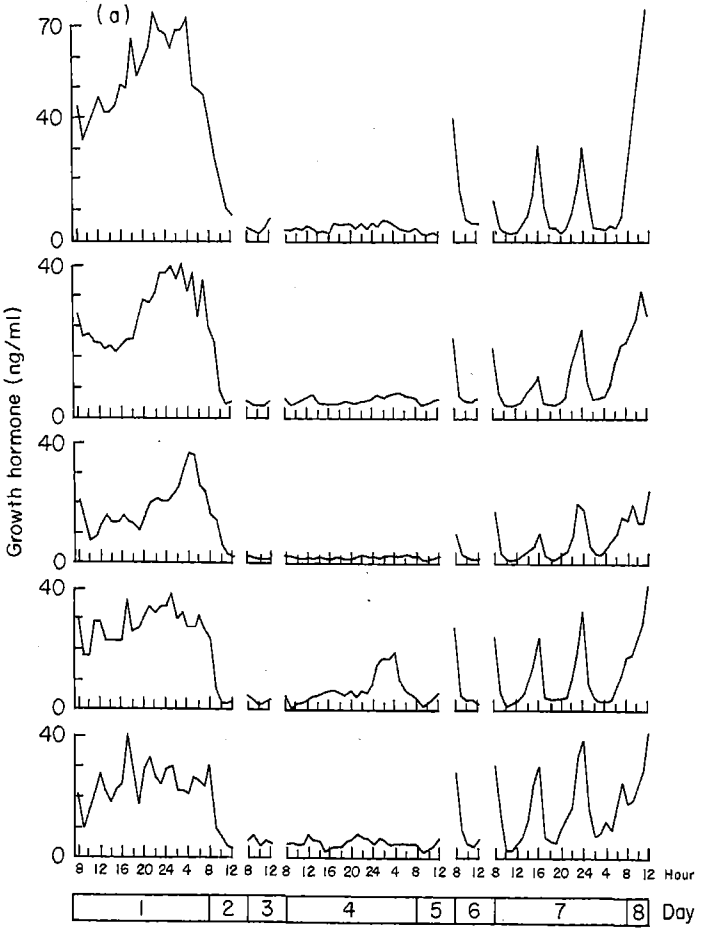

Figure 27. Serum GH profiles in 5 acromegalic patients examined hourly before (day 1); during continuous sc pump infusion of 100 µg/24 h octreotide (day 2, 3 and 4); and during sc injections of 33 µg octreotide at 0800, 1600 and 2400 h (day 5, 6 and 7). Samples were obtained from 0800 to 1200 h at day 2, 3, 5, 6 and 8; and from 0800 to 0800 h at day 1, 4 and 7. (Adapted from Christensen SE, Weeke J, Orskov H, Moller N, Flyvbjerg A, Harris AG, Lund E, Jorgensen J [44]).

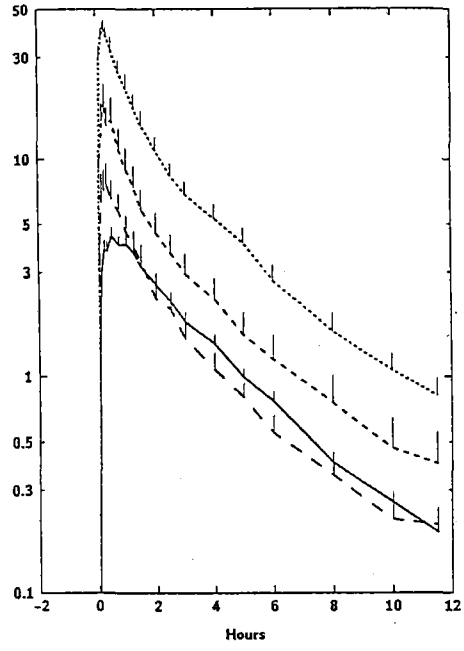

Figure 28. Average serum octreotide levels (y-axis) (±SEM) in 13 patients with acromegaly after different applications of octreotide. Note the faster resorption phase after nasal insufflations and the similar AUC after sc injection of 100 µg octreotide (solid line) and after nasal application of 500 µg octreotide (thick dashed line). Other dashed lines indicate 1000 µg (- - -) and 2000 µg (.....) intranasal octreotide doses (Adapted from Weeke J, Christensen SE, Orskov H, Kaal A, Pedersen MM, Illum P, Harris AG [52]).

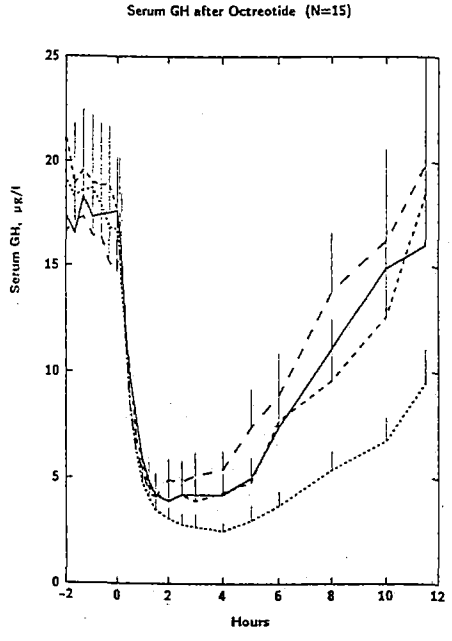

Figure 29. Average serum GH patterns (±SEM) in 15 patients with acromegaly after different applications of octreotide via subcutaneous injection and nasal insufflation. Note the similar suppressive effects of octreotide after sc injection of 100 µg (solid line) and after nasal insufflation of 500 µg (-- -- --) and 1000 µg (- - -) of octreotide. The dotted line (.....) refers to the effects of the 2000 µg dose of octreotide (Adapted from Weeke J, Christensen SE, Orskov H, Kaal A, Pedersen MM, Illum P, Harris AG [52]).

Parameters	100 µg sc intranasal	500 µg intranasal	1000 µg intranasal	2000 µg intranasal	P
$t_{1/2}$ K a min	24.1 ± 2.5	11.3 ± 1.9 [b]	7.9 ± 1.6 [b]	7.1 ± 1.6 [b]	< 0.0001
$t_{1/2}$ a min	11.3 ± 1.9	12.9 ± 1.9	17.3 ± 2.5	21.3 ± 3,8 [b,c]	< 0.02
$t_{1/2}$ ß min	169 ± 20	148 ± 17	155 ± 57	208 ± 26	ns
tmax min	42.3 ± 5.4	16.5 ± 1.6 [b]	13.5 ± 1.8 [b]	13.8 ± 1.8 [b]	< 0.0001
Max µg/L	4.5 ± 0.4	8.7 ± 1.9	20.8 ± 4.2 [b, d]	43.4 ± 2.8 [b,c,e]	< 0.0001
F		0.22 ± 0.03	0.22 ± 0.05	0.27 ± 0.03	ns
AUC (0-690 min) µg L/min	896 ± 81	957 ± 168	1923 ± 439 [b,d]	4597 ± 536 [b,c,e]	< 0.0001

Table 10. Pharmacokinetics of nasal and injectable octreotide. Results are presented as mean ± SEM, n =13 patients. Ns = non significant
[a] Analysis of variance, multiple range tests by least significant difference procedure.
[b] P < 0.05, 100 µg sc vs. intranasal 500 µg or 1000 µg or 2000 µg.
[c] P < 0.05, 500 µg intranasal vs. 2000 µg intranasal.
[d] P < 0.05, 500 µg intranasal vs 1000 µg intranasal.
[e] P < 0.05, 1000 µg intranasal vs. 2000 µg intranasal.
(Adapted from Weeke J, Christensen SE, Orskov H, Kaal A, Pedersen MM, Illum P, Harris AG[52])

Given the lack of a feasible oral formulation and in an effort to improve the convenience of administration, the LAR depot form of octreotide was produced. As mentioned above, the approach taken was to emulate the excellent 24-hour GH control achieved with continuous sc. infusion. This process began while we were running the clinical development program but the clinical studies were performed, analysed and reported later on. In summary, LAR octreotide consists of the drug incorporated into biodegradable DL-lactide-co-glycolide polymer microspheres that are injected intramuscularly and slowly release effective doses of octreotide over a period of weeks. Octreotide LAR reduces GH/IGF-1 secretion effectively when administered once every 28 days at a dose of 3-30 mg[53,54]. GH was persistently suppressed during the plateau octreotide concentration phase on days 14-42, with consistent stable inhibition of GH secretion beginning with the third monthly dose of octreotide. In patients who had a good response to intermittently injected octreotide, 79.5 % experienced a drop in GH levels to <2 µg/L, with 67.9% demonstrating normalisation of IGF-I levels. All patients experienced an improvement in their clinical signs and symptoms (headache, sweating, fatigue, joint pain, carpal tunnel syndrome and paraesthesia). Recently, LAR octreotide has been compared in head-to-head trials with another long acting depot somatostatin analogue, lanreotide slow release (SR)[55]. The authors found that octreotide LAR was more effective in terms of GH and IGF-1 control when administered once monthly than lanreotide SR given twice to three times per month. The better efficacy of octreotide LAR was due to its more favourable pharmacokinetic profile, which facilitated sustained release of octreotide over a period of 30 days, compared with lanreotide that required administration every 10 - 15 days. The LAR and SR formulations of somatostatin analogues have become very popular, however intermittent injections are still widely used. Razzore et al, highlighted in a recent retrospective study that improved GH and IGF-1 control occurred with intermittent sc. octreotide (150 - 600 µg/day) compared with lanreotide SR (30-60 mg intramuscularly every 10-14 days) during six months of treatment[56]. They suggested that patients undergoing pre-surgical somatostatin analogue treatment use intermittent octreotide therapy.

IV.IV - REGULATORY APPROVAL OF OCTREOTIDE

The data concerning the 178 acromegalic patients was compiled and a dossier submitted in 1987 to various European regulatory authorities. Regulatory approval for the use of octreotide in the treatment of acromegaly followed in 1989. The approval process in the U.S. was not as straightforward as that we experienced in Europe. In late 1987, approval was sought for GEP tumours (including glucagonomas, gastrinomas and insulinomas) and acromegaly together, however, as described elsewhere, the FDA restricted approval to symptomatic carcinoids and VIPomas. A multicentre randomised double blind placebo-controlled trial was implemented in the US, in contrast to the more direct approach allowed by the European regulatory authorities. Data was eventually presented to the FDA from a prospective North American placebo-controlled, multicentre trial of octreotide (100 or 250µg sc every 8 hours) in 115 acromegalic patients[57]. Integrated mean GH levels were reduced to <5µg/l in 49 - 53 % of patients and IGF-1 levels were normal in 55-68% of patients. They also found that the higher dose of octreotide (250 µg sc every 8 hours) did not improve biochemical control significantly. In summary, octreotide (100µg every 8 hours) decreased GH to <5 µg/L in approximately 50% of patients, while 85 - 90 % of patients experienced a significant drop in GH secretion. IGF-1 levels were also well controlled by octreotide, with normal levels noted in 40 - 70% of patients treated. Together with Ezzat and colleagues, we examined the effects of different octreotide doses in 99 patients with acromegaly and determined that for 50% of patients a dose of 300 µg/day of octreotide was sufficient, although some patients required a small dose escalation (*Figures 30, 31*)[58]. It is interesting to note that the

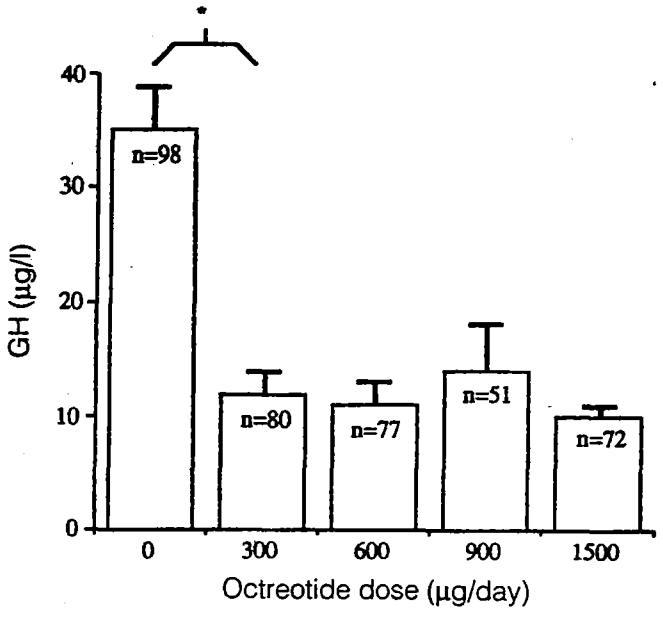

Figure 30. Growth hormone levels in response to escalating doses of octreotide. Mean GH concentrations are shown in response to increasing amounts of octreotide administered subcutaneously in 3 divided daily doses of 100, 200, 200 and 500 µg. Blood was sampled immediately before and after an injection every hour for 12-24 h to obtain mean GH determinations. *p<0.001 indicates that comparisons between baseline and each dose of octreotide were statistically significant. (Adapted from Ezzat S, Harris AG, Gnehm M, Ferber G, Boerlin V [58]).

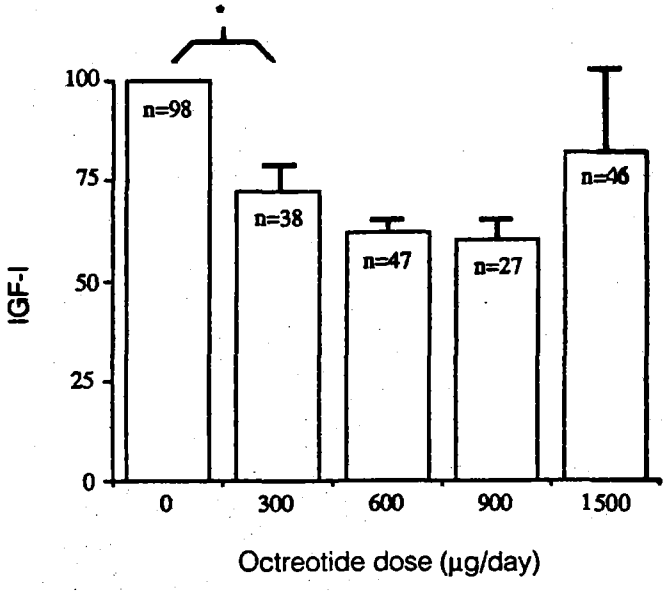

Figure 31. IGF-1 levels in response to escalating doses of octreotide. Shown are IGF-1 levels expressed as percentage of their respective baseline values. Octreotide was given subcutaneously in 3 divided doses of 100, 200, 300 and 500 µg. *p<0.001 indicates that comparisons between baseline and each dose of octreotide were statistically significant. (Adapted from from Ezzat S, Harris AG, Gnehm M, Ferber G, Boerlin V [58]).

eventual findings of the North American randomised trial and the dose-ranging study match well with the results of not only our European-based prospective trials, but indeed with the original retrospective case collection. The FDA finally approved octreotide for use in acromegaly in 1994. Long term U.S. experience with octreotide in acromegaly has been published since its approval in 1994. Newman et al reported safety and efficacy data from 103 acromegalic patients treated with octreotide (300 - 1500 µg s.c.) for a mean duration of 24 months [59]. GH levels fell from 30.9µg/l to 5.7 µg/l after three months and remained suppressed, while plasma IGF-1 concentrations were normal at < 50% of the assessment periods in 64% of patients treated for 12-30 months. No evidence of patients developing gradual resistance to octreotide was noted.

Following on from the valuable data derived from the original 178 patient retrospective analysis [60], many subsequent trials have assessed the marked effect on patients symptoms and signs in acromegaly. Large studies have shown that octreotide treatment improves signs and symptoms of acromegaly dramatically, in many cases before the improvement in biochemical parameters is significant. Headache, soft-tissue swelling, arthralgia, fatigue and hyperhidrosis improve in up to 95% of acromegalic patients treated with octreotide, and improvement is often seen within the first few days of administration.

As part of MJ Forster's doctoral thesis, I was co-supervising we developed the data collection undertaken for the Clinical Development Program in acromegaly into the largest descriptive collection of acromegalic patients [61]. We defined the clinical and biochemical features of

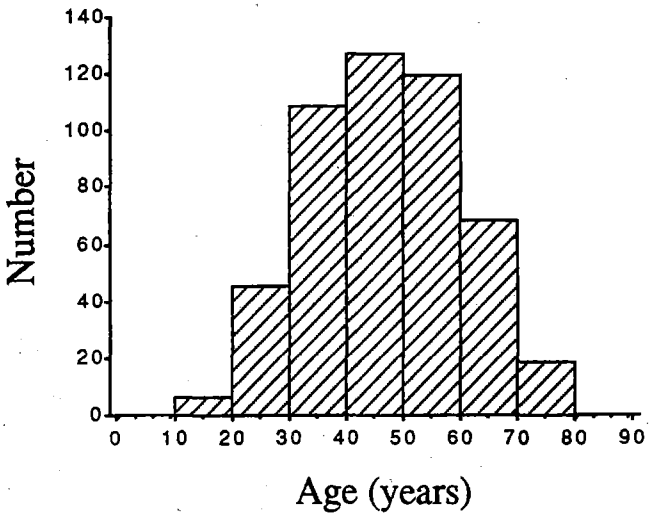

Figure 32. Age distribution by decade of 500 patients with acromegaly. (Adapted from Ezzat S Forster MJ, Berchtold P, Boerlin V, Redelmeier, Harris AG [61]).

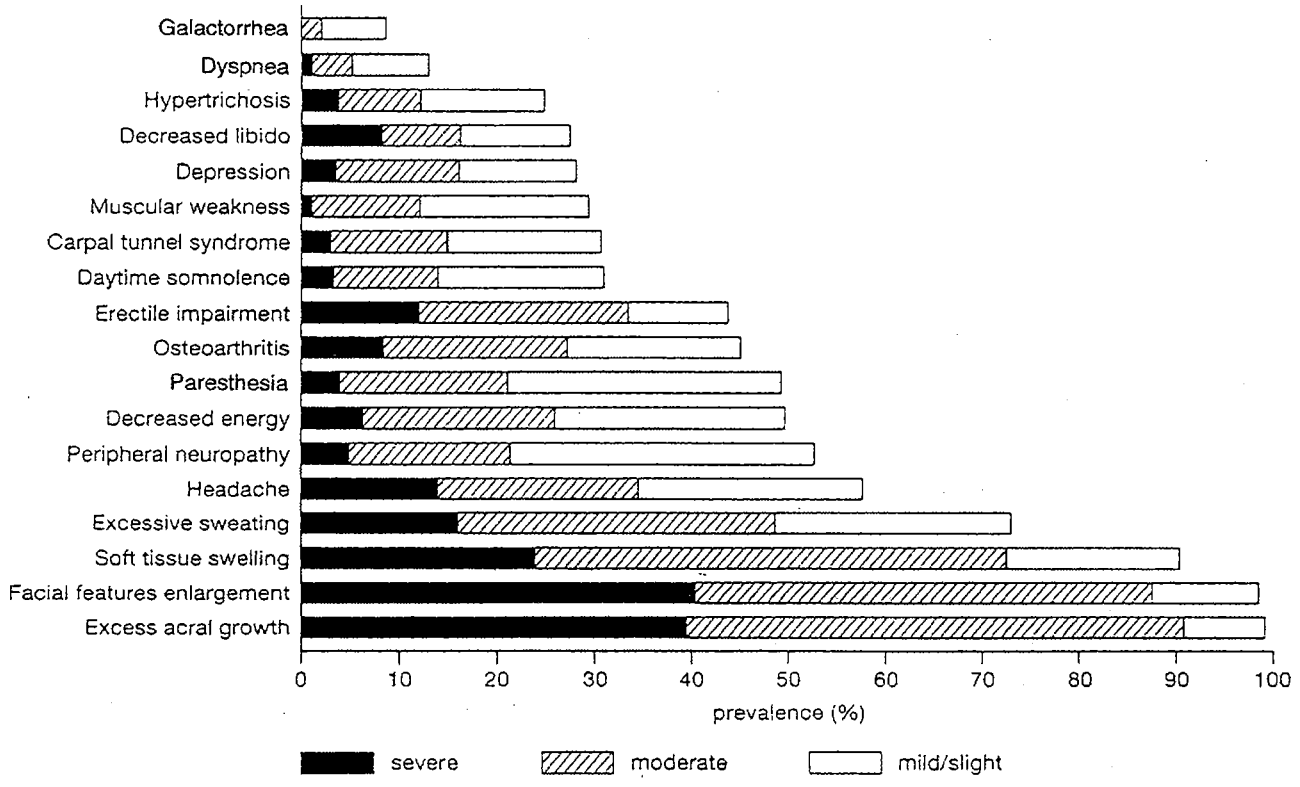

Figure 33. Prevalence of various signs and symptoms in 500 patients with acromegaly. Severe features are represented by solid histograms, moderate by diagonally hatched and mild/slight features by open histograms. (Adapted from Ezzat S, Forster MJ, Berchtold P, Boerlin V, Redelmeier, Harris AG [61]).

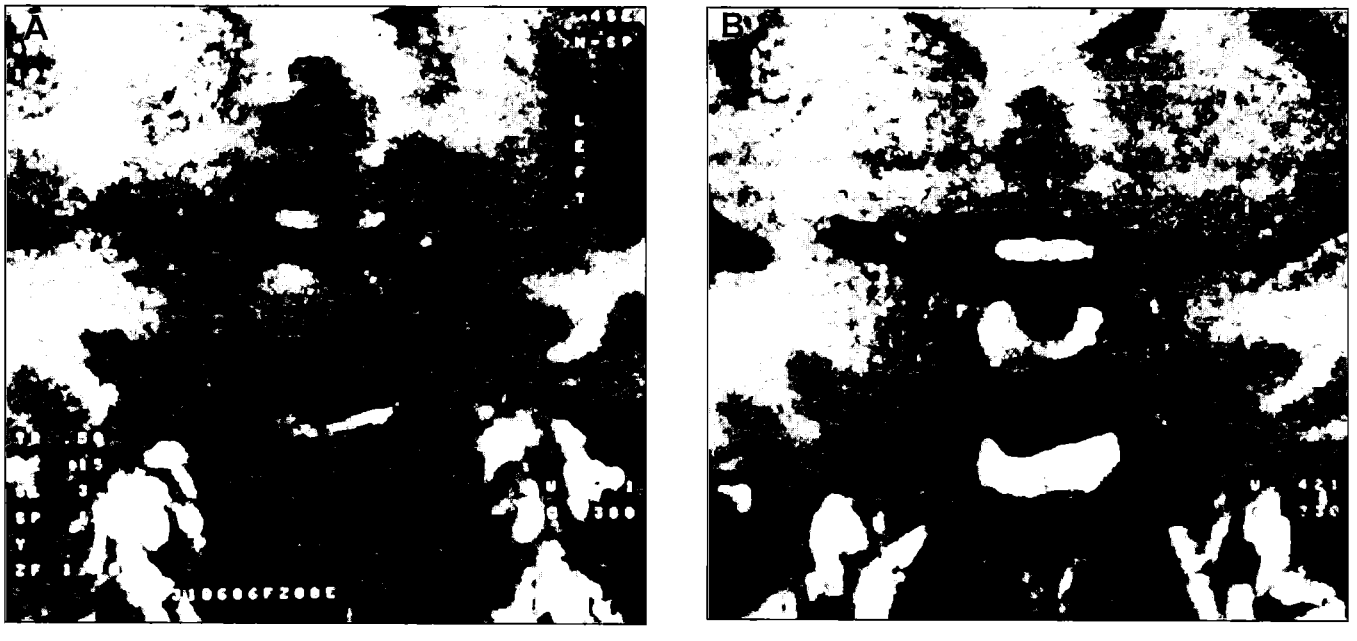

Figure 34. Magnetic resonance images (MRI) of a pituitary macroadenoma one month before (above) and four months after (below) initiation of octreotide therapy. (Adapted from Stevenaert A, Harris AG, Kovacs K, Beckers A [64]).

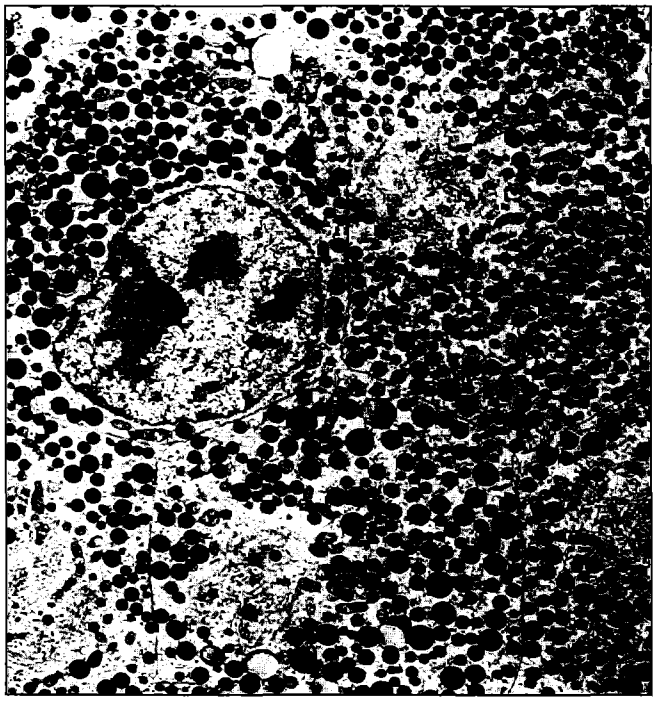

Figure 35. GH cell adenoma of a patient treated with octreotide. The cells are somewhat smaller than normal, the nucleus contains more heterochromatin, and the size and number of secretory granules are increased. Morphological changes in the pituitary tumours of octreotide-treated acromegalic patients are heterogeneous and the above figure is not illustrative of either "typical" changes nor does it catalogue all changes that are seen pathologically. Magnification x 4900. (Adapted from Ezzat S, Horvath E, Harris AG, Kovacs K [72])

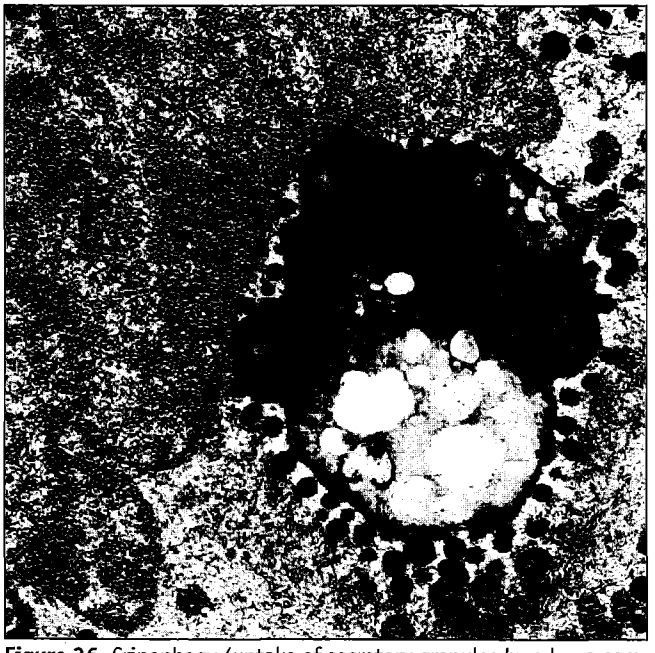

Figure 36. Crinophagy (uptake of secretory granules by a large complex lysosomal body) is depicted in a GH cell adenoma from an octreotide-treated patient. As noted in the previous figure, octreotide-associated morphological effects in GH-secreting pituitary tumours are heterogeneous and this figure is merely illustrative of one notable feature. Magnification x 12,400. (Adapted from Ezzat S, Horvath E, Harris AG, Kovacs K [72])

acromegaly in 500 individual patients, thus providing in the context of an industry setting a unique higher educational opportunity that led to the awarding of Dr. Forster's M.D. degree. (Publications with Annie Wagenaar [35] and Brenda Koop *(see Chapter VII)*) were also the result of collaborative research that was performed during their internship at Sandoz on the clinical effects of octreotide in acromegaly. The mean age at diagnosis was approximately 40 years in both men and women and acromegaly occurred equally in both sexes (*Figure 32*). Obesity and hypertension were present in 75 % and 50% of patients, respectively. Impaired glucose tolerance was diagnosed in 36%, while nearly a third of patients were diabetic. Hyperprolactinaemia was noted in 18% of patients. Symptoms and signs like acral growth, soft tissue swelling, and hyperhidrosis were present in the majority (98%) of patients (*Figure 33*). Such large-scale data collections are rare in acromegaly, and our study remains the largest case collection to date. Recently Katznelson and colleagues reported an acromegaly registry pilot study of hypogonadism in acromegalic patients [62]. This internet-based registry of data collected information retrospectively on 363 patients between 1976 and 1996, compared with our collection of 500 patients. The dynamic relationship fostered between the clinical development group at Sandoz and the various academic research groups thus allowed us to collect, analyse and disseminate data on acromegaly that has helped to deepen our understanding of the characteristics of the disease.

Early during the process of collecting data on the compassionate use of octreotide in acromegaly, we noted significant effects on pituitary tumour size [63] in our series of 189 acromegaly patients, pituitary tumour size decreased by greater than 20% in 15 (44%) of 24 patients [28]. Subsequent studies have used tumour size as an outcome measure, but the effects of octreotide are heterogeneous. Up to 50% of patients have smaller tumours after octreotide therapy [64] (*Figure 34*), but the magnitude of shrinkage is very variable (10-80%) [65,66,67,68,69,70,71]. The morphology of the tumour may also change during octreotide treatment making it softer and easier to remove surgically. With Ezzat et al we reported that the GH inhibitory effects of octreotide were significantly better in patients harbouring adenomas with densely granulated somatotroph cells, compared with those harbouring sparsely populated somatotrophs [72]. This was confirmed by Stefaneanu et al, who reported that GH and somatostatin receptor subtype 2 (SSTR2) messenger RNA signals were mildly decreased in densely granulated somatotroph cells from patients treated with octreotide, compared with somatotroph cells from untreated patients [73]. However, the effects of octreotide on tumour morphology appears to be variable, as in another study with Ezzat et al, we found that no consistent morphological change typified the effect of octreotide [74]. Changes we noted included variations in secretory granule number and size, cell size, nuclear characteristics among others *(see Figure 35, 36 for illustrative examples)*. This variability may explain the poor correlation between GH suppression, immunohistological characteristics and pituitary tumour shrinkage in patients with acromegaly treated with octreotide, as noted by Plöckinger et al. [75].

Major cardiorespiratory morbidities associated with acromegaly have improved with octreotide therapy. Most significant among these is cardiomyopathy[76,77,78]. With Chanson and colleagues, we demonstrated that the improvement in cardiac status can occur as soon as within a few weeks of starting octreotide[79]. Others have shown left ventricular hypertrophy in particular has decreased with octreotide[80] and this decrease has been associated with improved cardiovascular filling parameters and enhanced exercise tolerance[81,82]. Colao et al recently reported similar improvements in left ventricular wall thickness within three months of starting octreotide LAR therapy[83]. Interestingly, only the patients that achieved normalisation of GH/IGF-1 exhibited significant improvement in left ventricular function. Hypertension and glucose intolerance, common in acromegaly, correlate independently with the severity of acromegalic cardiomyopathy[84]. Even in normotensive acromegalic patients, baseline and dynamic noradrenalin responses are abnormal[85]. In response to octreotide infusion, basal noradrenalin secretion and catecholamine response to posture normalised. Abnormal catecholamine responses may play a role in hypertension and cardiovascular disease in acromegaly and may represent one mechanism of action of octreotide in this regard. Sleep apnoea has also been shown to improve on octreotide therapy through a reduction in pharyngeal/palatal soft tissue swelling and hence decreased upper airway resistance[86].

Mortality in acromegaly is mainly due to cardiovascular disease. We have studied two of the main determinants of cardiovascular mortality, namely lipids and regional haemodynamics. With Cohen and colleagues, we treated 17 patients with active acromegaly with octreotide 100-500 μg three times a day sc for three months[87]. At the end of treatment, GH and IGF-1 had fallen by 61% and 36% respectively, while insulin levels fell by 42%. Total cholesterol fell over the treatment period, but not significantly. In contrast, mean triglycerides fell from 2.2 ± 0.4 mmol/L to 1.6 ± 0.3 mmol/L ($p<0.05$) during octreotide treatment. An interesting phenomenon was noted in this study: patients with diabetes mellitus had higher triglycerides and GH levels before treatment, and the effect of octreotide on these parameters was significantly ($p<0.05$) less than in non-diabetic patients. Acromegalic patients commonly suffer from diabetes mellitus, and it appears that the complex metabolic/counter-regulatory hormonal disturbance associated with diabetes mellitus leaves these acromegalic patients less responsive to octreotide, although this issue requires further investigation. With respect to regional blood flow, we again collaborated with Chanson and colleagues in France to describe cardiovascular disturbances associated with acromegaly[88]. This collaboration had begun during the Clinical Development Program for octreotide in acromegaly, and the academic relationship has lasted for many years since our first work together. In 12 active acromegalics patients, we found cardiac index and stroke volume to be higher than normal values. Importantly, mean arterial blood pressure was higher in acromegalics patients, while brachial mean arterial velocity and blood flow were significantly higher and lower than normal, respectively. We found a negative relationship between IGF-1 and brachial arterial blood velocity and a positive linear relationship between IGF-1 and mean blood flow. The results of this study, published in 1998, suggest that cardiovascular disturbances in acromegaly are not simply limited to the heart, but also effect regional blood flow in a heterogeneous fashion.

IV.V - Advances in Current Research

Acromegaly remains an area of active research for octreotide and other somatostatin analogues. Long-term studies with sc injectable and LAR octreotide have demonstrated safety and continued efficacy over years of treatment. Many of the criteria that were studied as part of the Clinical Development Program for octreotide have been expanded upon by other research groups. A recent development that will be useful in assessing the long-term efficacy of various treatments, including octreotide, is the publication of a partially validated acromegaly quality of life questionnaire, called ACROQOL[89]. Most other diseases have been studied with this type of tool, which can measure more complex -often termed "soft"- endpoints that assess the impact of the disease on the patients daily life. Full validation of the ACROQOL will require pre- and post-treatment application of the questionnaire to large numbers of patients with acromegaly across many countries. It will be particularly interesting to compare the impact of surgical and medical therapies on the ACROQOL and its correlation with GH and IGF-1 levels before and during therapy.

Comparative studies between octreotide LAR and lanreotide slow release (SR) have become more common as the use of both drugs has increased in the clinical setting. Ronchi et al compared the effects of octreotide LAR and lanreotide SR in 10 patients with acromegaly, two of who had diabetes mellitus. Octreotide LAR was more effective than lanreotide SR at reducing GH and IGF-I[90]. The most recent data available on octreotide LAR concerned its effect as primary therapy on hormonal and tumour size parameters in 27 patients with acromegaly treated in nine centres in the United Kingdom[91]. Patients received octreotide 100-200 μg s.c. tid for 24 weeks after which time 16 patients switched to octreotide LAR monthly for 24 weeks. All patients experienced tumour shrinkage after s.c. octreotide for 24 weeks (mean tumour volume reduction 43-49%), while patients treated with octreotide LAR for another 24 weeks subsequently experienced a mean tumour volume decrease of 24%. GH levels were below 2.5 μg/L in 79% of patients, while IGF-1 levels normalised in 53% after 48 weeks of therapy. A high dose preparation of lanreotide SR (60mg every 3 to 4 weeks) has been made available to overcome the dosing problems associated with lanreotide SR 30mg, which required an intramuscular injection every 10 days[92]. Despite the dosage increase no improvement in the rate of GH and IGF-I normalisation was noted. In a parallel effort to improve patient acceptability of lanreotide SR, a water-based, low volume 30mg "autogel" preparation has recently been developed. Lanreotide autogel 30mg administered every 4 weeks

by deep subcutaneous injection has been reported to be as effective as lanreotide SR 30mg given once every 7-14 days in lanreotide-responsive patients[93].

Thyroid disease is considered to occur with increased frequency in acromegaly. The physical and morphological effects of excess GH/IGF-I on the thyroid gland have been studied in depth by Bogazzi et al[94]. Active acromegaly was associated with increased thyroid vascularity (as reflected by increased colour Doppler ultrasound blood flow), which was found to resolve in the overwhelming majority of patients after treatment with octreotide or lanreotide. Disease activity in acromegaly has also been assessed indirectly by a dermatological method. It is known that acromegalic patients have increased skin thickness and elasticity, and Braham et al measured skin tensile properties in 13 patients with acromegaly compared with controls. They reported that skin distensibility/elasticity (as measured at the forearm and neck by a computerized device) was consistently higher in the acromegalic population. Furthermore, skin distensibility correlated positively with the patients' highest historical IGF-I levels and negatively with post-treatment (surgery, octreotide or both) IGF-I[95].

The effects of somatostatin analogues on pituitary tumour characteristics continues to be an issue of interest to neurosurgeons and endocrine pathologists. Losa and colleagues noted that octreotide treatment was associated with a lower level of proliferation in resected GH-secreting tumours compared with specimens taken from acromegalic patients who had not received octreotide before surgery[96]. Contrary to our findings with Ezzat and colleagues[72], no difference in the index of apoptosis was seen, which indicates that the mechanism of action of octreotide in suppressing pituitary tumour cell activity (tumouristatic versus tumouricidal) remains the subject of debate. In a comparative study, Amato et al found that both octreotide LAR and lanreotide SR induced significant tumour shrinkage (approximately 30% volume reduction) in previously untreated acromegalic patients[97]. At 12 and 24 months' follow up, no differences between the two treatments had emerged and the mean magnitude of tumour shrinkage remained approximately 30%. Effects in the study were considered to be more pronounced in patients with macroadenomas than microadenomas. The recently-introduced high-dose lanreotide SR 60mg has also been shown to induce tumour shrinkage in a small series of acromegalic patients[98].

The impact of somatostatin analogues on the heart has been studied extensively in recent years, because as noted above cardiovascular pathology is the major cause of death in the acromegalic population. The importance of the deleterious effects of GH and IGF-I on the heart has been underpinned recently by Colao et al[99]. This group described the effects on the cardiovascular system of short-term and long-term GH-excess due to acromegaly. They found that patients with acromegaly for less than or equal to five years had increased carotid artery intimal thickness, which decreased significantly after six months' treatment with octreotide LAR. Similarly, raised heart rate and increased ejection fraction fell with octreotide LAR therapy, as did left ventricular mass. Biochemical abnormalities, including insulin, total cholesterol and fibrinogen levels all decreased with octreotide LAR, while high-density cholesterol rose concomitantly. This study demonstrates that important deleterious cardiovascular effects can occur even after acromegaly of relatively short duration. The significant effect of octreotide LAR on these physical and biochemical parameters reinforces the benefit of both early diagnosis and treatment. The same group reported a similar decrease in carotid arterial intimal thickness and a favourable alteration in cholesterol abnormalities with lanreotide SR treatment for six months in 24 acromegalic patients with active disease (but not stratified according to duration of disease)[100]. However, in a small study involving acromegalic patients, patients with GH-deficiency and healthy controls Irving et al concluded that GH excess and deficiency had only a modest effect on peripheral vascular pathology[101]. This group noted lower numerical baseline and higher post-ischaemic forearm blood flow in acromegalic patients, although no difference between acromegalics and controls was seen in terms of blood pressure. It should be noted that cardiac output was not measured in the acromegalic group, which, along with the failure to include patients with and without associated diabetes mellitus represents a weakness that should be addressed in other studies. These differences in patient characteristics may explain the divergence between the results obtained by this group and our results with Chanson et al.[88]. Cardiac abnormalities have also been shown to resolve partially following transsphenoidal resection of pituitary adenomas, while combination octreotide and surgical therapy may also achieve help patients to achieve cardiac benefits[102,103].

In the time since the Clinical Development Program, a greater understanding of the importance of inflammatory mechanisms in the pathophysiology of cardiovascular disease and cancer has been achieved. The role played by macrophages and other leukocytes in atherosclerosis is now acknowledged as being core to the development and promulgation of the disease. Light is currently being shed on how GH excess can influence immune mechanisms in acromegaly and its associated co-morbid conditions. Mice with GH excess have greater thymic and splenic weight, which appears to impact on immune responses to lipopolysaccharide and other mitogens[104]. In patients with active acromegaly, increased T cell (CD3, CD4) and decreased B cell function (CD19) has been reported[105]. This lymphocyte subtype alteration may play a permissive role in certain pre-cancerous conditions, such as, colorectal polyps[106] and prostatic hyperplasia[107], respectively.

The field of medical therapy in acromegaly has broadened with the introduction of the specific GH-antagonist, pegvisomant. This drug, which prevents GH-mediated GH receptor activation, has been shown to normalise IGF-I levels in a majority of patients studied[108]. Like any new drug,

safety issues remain important until large numbers of patients have been treated in the daily clinical setting. In terms of pegvisomant, concerns have been raised regarding tumour expansion during pegvisomant treatment of acromegaly in one patient [109]. Moreover, the beneficial effects of octreotide on vascular pathology and cholesterol abnormalities have not been shown with pegvisomant; indeed pegvisomant may actually alter cholesterol profiles adversely [110]. The development of pegvisomant has also permitted basic investigation of control of the GH axis, and has revealed interesting new information regarding the roles of ghrelin, GHRP-6 and GHRH at central and peripheral sites [111, 112, 113] and in pathological states [114]. Regarding ghrelin, this important GH regulator, the importance of which was not recognized at the time of the Clinical Development Program in acromegaly has very recently been shown to be modulated by somatostatin [115] and octreotide [116] in humans. The impact of somatostatin-dependent ghrelin modulation on disease status in acromegaly remains to be determined.

Finally, despite consensus on the pathological role of GH in acromegaly, there continues to be uncertainty as to precisely what level of GH represents a biochemical diagnosis and what do we mean by the term "cure" [117, 118]. Refinements in laboratory techniques continue apace, particularly in terms of more precise immunoassays. Costa and colleagues reported results of an extensive profiling study using a highly precise immunoassay that studied GH levels following a standard oral glucose tolerance test [119]. It appears that of 32 treated acromegalic patients, only five (15.6%) achieved a "normal" GH nadir level of 0.25 μg/L. However, the authors noted that a post glucose tolerance test GH level of 1μg/L was associated with normal age-corrected IGF-1 levels. This indicates that a nadir GH of 1 μg/L may be more desirable as a goal for biochemical cure than previous higher levels of 2.5 μg/L or even 5 μg/L. Consensus guidelines for the treatment of acromegaly have been updated in 2002, and provide confirmation of the central role of somatostatin analogues, including octreotide, as the "mainstay of medical therapy" for acromegaly [120] (*Figure 37*).

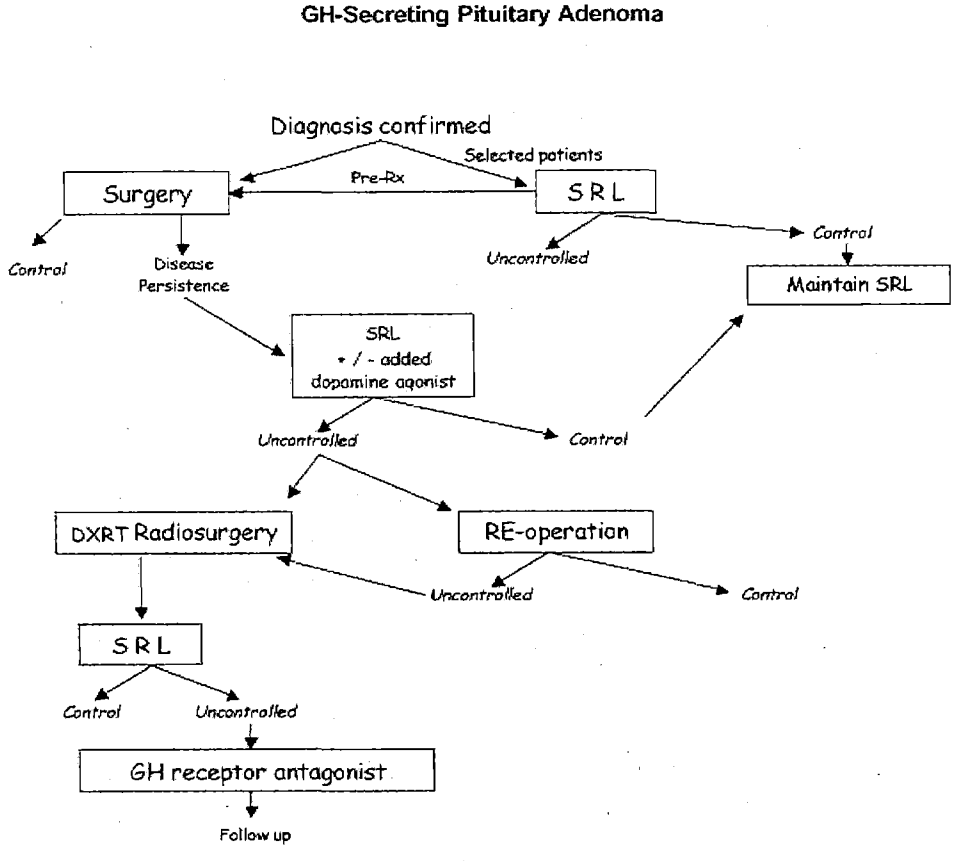

Figure 37. Diagrammatic representation of treatment approach for newly diagnosed GH secreting pituitary adenomas. DxRT = Direct beam radiotherapy; SRL=somatostatin receptor ligand (e.g. octreotide). Adapted from Melmed et al [120]

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Chapter V.

The Clinical Development of Octreotide in Gastroenterological Diseases

V.I - GASTROENTEROPANCREATIC (GEP) TUMOURS

V.I.I - Characteristics of GEP Tumours

The term "gastroenteropancreatic (GEP) tumours" refers to a diverse group of tumours that arise due to hyperplasia or malignancy of hormone producing cells in the gut. Some cells are concentrated in organs, such as, the pancreas and others are scattered throughout the gastrointestinal tract. Hormones produced by this family of cells are potent regulators of gut motility and secretion and include 5-hydroxytryptamine (5-HT), glucagon, insulin, gastrin, vasoactive intestinal polypeptide (VIP), pancreatic polypeptide (PP) and motilin. Over-production of one or more hormones due to adenoma/carcinoma can cause serious and debilitating effects, such as, secretory diarrhoea (diarrhoea which persists with fasting), flushing, hypotension, cardiac valvular disease and rashes. All GEP tumours are rare, and many are slow growing, only becoming evident clinically after they metastasize to the liver and secrete hormones into the systemic circulation by escaping hepatic first-pass metabolism. The incidence of carcinoid tumours alone is about 5 per million population per year [1], while other GEP tumours, such as VIPomas (0.05 - 0.2/million) and glucagonomas (0.01 - 0.1/million) occur with even less frequency [2].

Somatostatin is also a gut endocrine peptide, formed by cells of the GEP system in the pancreas and diffusely along the gut and is a natural inhibitor of most other GEP hormones. As noted in previous chapters, somatostatin decreases the secretion of enzymes and fluid from the gut by inhibiting the release of the hormonal stimulators of these actions. In addition, somatostatin can suppress the activity of muscles in the wall of the gut, thereby slowing the transit of food between different regions of the digestive tract. In 1978, Thulin et al published a report in The Lancet regarding the use of natural somatostatin in the rescue of a patient with intra-operative hypotension due to GEP tumour hormonal hypersecretion (so-called 'carcinoid crisis') [3]. As before, the rationale for using octreotide in GEP tumours was based its longer half-life and more potent inhibition of hormone release, gut secretion and motility compared with short-acting native somatostatin.

V.I.II - GEP Tumours: The Compassionate Need Program

Before the advent of octreotide, treatment of GEP tumours such as carcinoids was limited to surgery and supportive care. The demand for octreotide for compassionate use in GEP tumours came from within the medical community, and was based upon the known inhibition by somatostatin of multiple gut peptide hormones. Clinicians viewed the increased inhibitory potency of octreotide relative to somatostatin as a clear indication that it could be of value in the treatment of their patients. Of central importance was the lack of effective therapies for certain patients suffering from GEP tumours. During this time octreotide was given out on a compassionate need, named patient basis at several centres worldwide through interaction between doctors and the local Sandoz affiliated companies. However, between 1984 and 1985, clinicians' demand for octreotide in compassionate need cases grew and initial feedback from its clinical use in GEP tumours was favourable.

Taking into consideration the logistical difficulties, the reported benefits to patients and the enthusiasm of the medical community, my colleague Dr. Michael Dunne with T. Fletcher at Sandoz in the United Kingdom, and Dr. Richard Elton, P. Hofker and J. Shui at Sandoz in the U.S., analysed data from individual cases for the purpose of gaining regulatory approval in the U.S. and worldwide. This data gathering process, which involved several hundred

patients with GEP tumours, could not have been performed without the existence of a cohesive multinational pharmaceutical company such as Sandoz. Similar to the case with acromegaly (*see Chapter IV*), detailed standardised case report forms were distributed and collected by the local Sandoz organization in each country, liaising directly with participating clinicians, following which the forms were returned to the octreotide clinical development group for analysis. The geographic spread of the participating centres was very wide, with 40 investigators in the U.S. and 38 investigators in 12 countries worldwide. The data collected demonstrated some heterogeneity in terms of rating of disease severity, hence, an internal standardised rating system was developed to provide a meaningful interpretation of the response to octreotide therapy compared with pre-treatment. This five-point scale is outlined below:

1 = symptom resolution or normalisation of measure (biochemical marker or clinical measure)
2 = symptom improvement or reduction in marker of 10% or greater
3 = no change
4 = symptom worsened or increase in marker of 10% or greater
5 = new symptom occurred

As noted by Dunne et al in their publication, overall improvement was judged as a mean rating of 1.5 - 2.4 on the above scale, while between 2.5 and 3.4 was judged as no overall change in disease severity. A full description of the methodology used to collect and analyse data in this case collection, such as, patient inclusion criteria, data recording and analysis, recommendations for octreotide administration and evaluation parameters are outlined in detail in published form by Dunne et al[4]. As indicated by Dunne et al in this series of patients with GEP tumours treated with octreotide, when the data collection process was completed in late 1986, 379 patients had received octreotide worldwide and full safety and efficacy information was available from 209 individuals. Many of these patients were extremely debilitated and had failed a number of alternate therapeutic alternatives. Therefore, much of the GEP tumour patient population treated with octreotide was in fact refractory to standard treatment. In 1987, a New Drug Application (NDA) was submitted to the FDA for octreotide based largely on the retrospective collection of uncontrolled assessments of safety and efficacy of octreotide in the management of patients with GEP endocrine tumours, including carcinoid tumours, VIPomas, glucagonomas, gastrinomas, GRFomas and PPomas. In September 1987, an FDA advisory board deliberated over the approval of octreotide as a treatment for symptomatic carcinoids and VIPomas. The FDA limited their approval of octreotide to the treatment of carcinoid tumours and VIPomas owing to the limited numbers of patients with other GEP tumours in the NDA submission. Important to the process of registration were the data from the largest single-centre subset that were treated at the Mayo Clinic in Rochester, Minnesota, USA by L Kvols and C Moertel[5,6]. Submissions by these senior investigators regarding the devastating and intractable nature of carcinoid syndrome and the benefits to patients afforded by octreotide therapy were extremely strong. Data were presented that indicated that octreotide treatment was associated with an improvement in diarrhoea and flushing in 74% and 87%, respectively, of patients with symptomatic carcinoids. Impressive results were also gained with VIPoma patients, 75% of whom experienced an improvement in their diarrhoea.

Of utmost importance in this process of registering octreotide was the close working relationship between senior investigators in the academic community and the extensive data-gathering structures available to Sandoz. The success of this process can be assessed from the extremely short period of time it took from the first compassionate use of octreotide in 1984 to full FDA registration in 1988. Preceding FDA approval, octreotide was approved for the treatment of GEP tumours in Europe and New Zealand in 1988.

Since its approval in the late 1980's, octreotide has become the treatment of choice for patients with carcinoids and other GEP tumours associated with secretory diarrhoea. On the whole, octreotide provides symptomatic benefits and large reductions in hormone secretion in over 50% of patients. We convened a group of experts in endocrinology, oncology, gastroenterology and surgery to participate in a consensus development conference in May 1993 to review pertinent dose-titration issues in the setting of approved indications, such as, carcinoid and VIPoma[7]. The recommendations of this consensus development panel are outlined in *Figures 38 and 39*. In many cases, the starting dose of 150 µg three times per day needs to be increased to combat expanding tumour bulk and rising hormone levels. Pathological studies have shown heterogeneous effects of octreotide on GEP tumour morphology, and many patients experience no decrease in tumour bulk. Despite dose escalation up to the milligram level, octreotide is well tolerated by patients with GEP tumours. In a review of the cost-effectiveness of octreotide in carcinoid and VIPoma, Schonfeld et al showed that octreotide was associated with a doubling of survival time in both conditions[8]. Furthermore, this doubling of survival was achieved with an almost negligible monetary cost (US $ 752.00 per year of life saved). As with acromegaly, a major inconvenience for patients was the multiple subcutaneous injections required for administration of octreotide. The LAR intramuscular form of octreotide (20 mg once monthly) demonstrated equivalent efficacy to three times daily subcutaneous injections in terms of hormone control and flushing symptoms[9]. The authors noted that the convenience of once monthly injections did not fully obviate the need for subcutaneous octreotide, which was useful at the beginning of LAR therapy until steady-state octreotide levels were reached. In conclusion, octreotide remains a standard option for the symptomatic treatment of GEP tumours[10], particularly in light of new evidence showing the majority of such tumours are somatostatin receptor subtype 1, 2, 3 and 5 positive[11]. Combination therapy with alpha interferon and octreotide continues to show promise for improving the suppression of both tumour growth and disease activity[12].

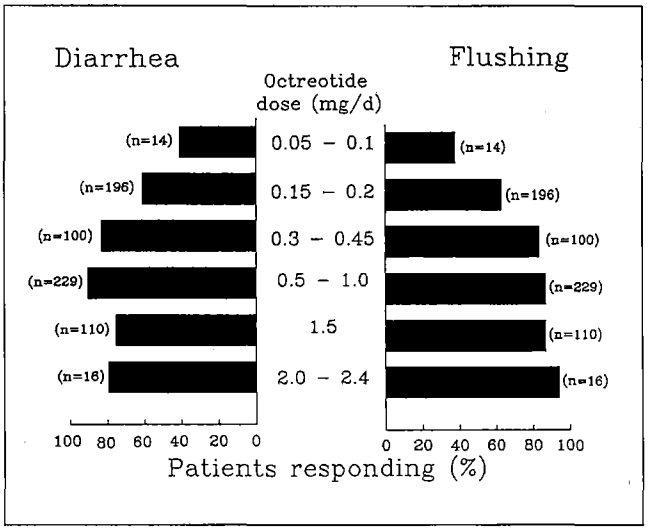

Figure 38. Relationship between octreotide dose and resolution of secretory diarrhoea or flushing in carcinoid syndrome patients. The figure demonstrates that maximum efficacy is obtained once patients' doses are escalated to between 300 and 450 µg per day. (Adapted from Harris AG, O'Dorisio TM, Woltering EA, Anthony LB, Burton FR, Geller RB, Grendell JH, Levin B, Redfern JS.[7]).

V.II - SECRETORY DIARRHOEA

V.II.I - Rationale for Octreotide Use

Somatostatin has multiple physiological effects in the gut, and it is heavily expressed in cells of the pancreas, visceral autonomic nervous system, endocrine cells, and gut lumen. Somatostatin is localised to the D cells of the pancreas and gut mucosa, particularly in the gastric fundus, antrum, and duodenum. D cells are situated in the lower third of the crypts, from where they extend cytoplasmic processes along the basal membranes to the basal pole of neighbouring glands. Thus somatostatin is well placed to exercise paracrine control of other endocrine cells in the gut. D cells also have microvilli in direct contact with the lumen, thus allowing changes in gut content to influence somatostatin release into either the gut lumen or the portal circulation. The gut is innervated by extrinsic and intrinsic somatostatin containing neurons, with the intrinsic neuronal activity being present in both the submucosal and myenteric plexuses. This widespread distribution explains how somatostatin can have multiple endocrine, paracrine, and exocrine functions within the gut. Somatostatin inhibits pancreatic endocrine and exocrine secretion, while suppressing secretion of stimulatory gastrointestinal hormones, and decreasing motility and splanchnic blood flow.

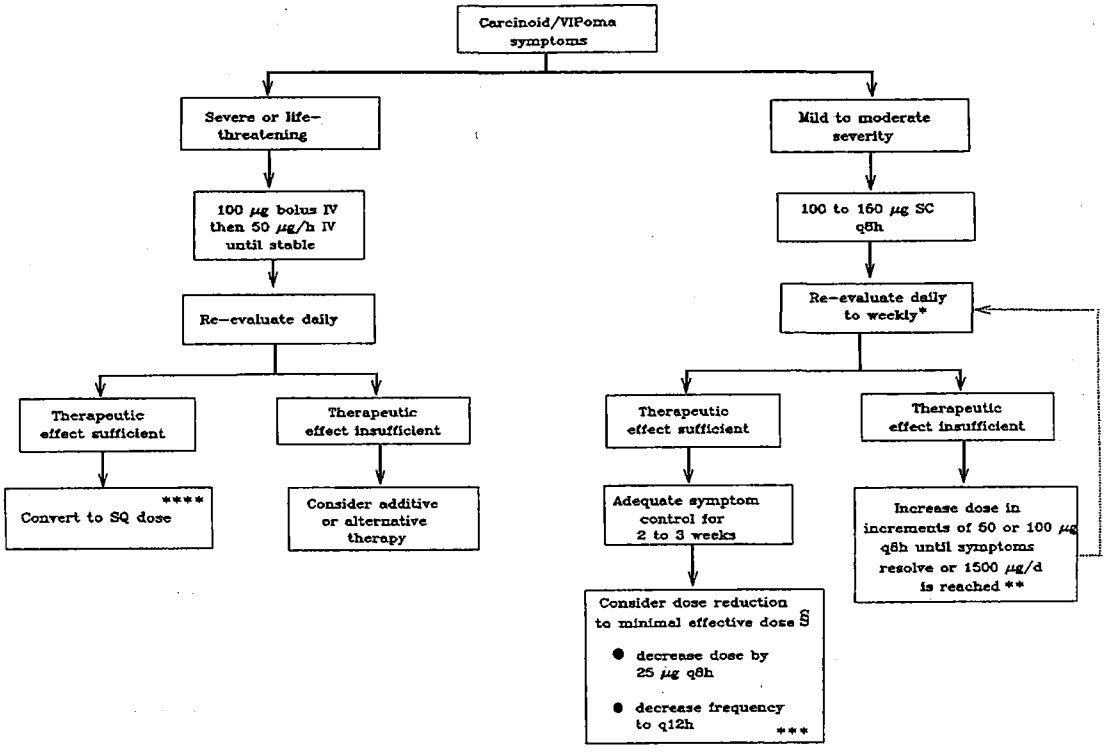

Figure 39. Algorithm for octreotide dose titration in patients with carcinoid syndrome or VIPoma-watery diarrhoea syndrome. * If symptoms warrant rapid control, re-evaluate daily. ** Dose escalation should occur in 50 µg increments up to 200 µg tid, then in 100 µg increments from 200 to a maximum of 500 µg tid. *** Maintenance dose should not be lower than 50 µg bid. **** Daily requirements delivered in three to four equal subcutaneous doses. (Adapted from from Harris AG, O'Dorisio TM, Woltering EA, Anthony LB, Burton FR, Geller RB, Grendell JH, Levin B, Redfern JS [7]).

As outlined in preceding chapters, octreotide exerts significant pharmacological effects on the gastrointestinal tract over and above those of native somatostatin. Octreotide decreases GEP hormone secretion, particularly glucagon, VIP, pancreatic polypeptide and gastrin. Octreotide inhibits pentagastrin-stimulated gastric acid secretion and is also a strong inhibitor of secretin/cholecystokinin-induced secretion of pancreatic enzymes and gallbladder contraction (reviewed in [13,14,15]). It has also been shown to accelerate or delay gastric emptying, prolong transit time at moderate to high doses, stimulate motility at low doses, and inhibit gallbladder emptying. Octreotide considerably increases intestinal transit time, and as a result, absorption of water and electrolytes is increased. Because of these effects on gut hormone and fluid secretion and motility, it was suggested that octreotide could be a valuable drug for the treatment of a wide range of gut hypermotility and hypersecretory disorders.

V.II.II - AIDS-Related Diarrhoea

V.II.II.I - Disease Characteristics

During the clinical development of the analogue in the treatment of GEP tumours, it was noted that octreotide had a potent effect on the severe secretory diarrhoea often experienced by these patients. Once this effect became apparent, it was decided to broaden the perspective and seek out other forms of secretory diarrhoea, which were not being adequately managed with existing treatments. Secretory diarrhoea was recognised as being common in patients infected with HIV/AIDS [16]. Given the major public health problem that AIDS represented in the 1980's - and continues to represent today - there was a great deal of interest in therapies that could alleviate conditions associated with the disease. In the era before the advent of antiretroviral combination therapy, patients with active AIDS infection often suffered from diarrhoea that was refractory to standard forms of therapy. Refractory AIDS-related diarrhoea can be extremely severe and is then associated with rapid weight loss and debilitation.

V.II.II.II - Clinical Experience with Octreotide in AIDS Diarrhoea

Based on its physiological action as a potent inhibitor of gastrointestinal secretion, physicians working with AIDS patients began to use octreotide on an individual case basis at centres in Europe and North America [17,18,19]. Once again, utilizing the cohesive data-gathering ability of Sandoz, the clinical development team began analysing the effect of octreotide in these scattered cases. In conjunction with Fanning and colleagues in Canada, we conducted a pilot study of the effect of octreotide on refractory HIV-associated diarrhoea [20]. We found that individual patients had experienced significant improvement in their diarrhoea after starting treatment with octreotide, which was well tolerated. Discontinuation of octreotide therapy was associated with a return of the patients' diarrhoea. The patient numbers in this study were small (11 evaluable patients) and the results were heterogeneous. Some patients experienced moderate stool volume reduction at octreotide doses of 150-750 μg/day sc. One patient remained on octreotide for as long as one year with good tolerability. Several other uncontrolled investigations suggested that octreotide was beneficial in the treatment of diarrhoea associated with AIDS. We designed and completed an open-label, prospective, multicentre trial in Canada and Europe to assess the effects of octreotide administered at doses ranging from 100 μg t.i.d. to 500 μg t.i.d. in 32 patients with AIDS-related refractory diarrhoea [21]. All recruited patients were refractory to common anti-diarrhoeal therapies and octreotide was administered at increasing doses up to 500 μg t.i.d. or until the patient responded to treatment. Of the 17 evaluable patients enrolled in this study, five were considered to be complete responders (<3 bowel movements per day) and 12 were partial responders (>50% reduction in stool weight). Another large open-label randomised trial in North America showed that of 51 patients, 21 (41.2 %) were considered to be partial or complete responders (>50% reduction in stool weight) [22].

Simon et al performed a double blind, placebo controlled U.S. multicentre outpatient study of octreotide therapy in HIV-infected patients with diarrhoea [23]. Following an initial baseline period, a three-week dose-escalation was performed with octreotide administered at 100 μg t.i.d. to a maximum of 300 μg t.i.d. based on the response to a 72 hour stool collection. The authors were unable to show statistically significant benefits of therapy using their regimen and study population, despite having more than 100 evaluable patients. Of the many possible reasons for a study with negative results, including actual lack of efficacy, the most obvious are heterogeneity in the study population and its treatment, inadequate sample size, and lack of strictness in the criteria for efficacy. Although most observers agree that chronic diarrhoea in patients with AIDS rarely remits spontaneously, especially in patients with CD4 lymphocyte counts of <50/mL, the authors found a 36% response rate to placebo in all placebo-treated patients and a response rate of 47% in patients whose condition was considered idiopathic. Inability to assure treatment compliance, including the dose of octreotide, the doses of other anti-diarrhoeal therapies, and complete stool collections also could have affected the results. The treatment design, which placed the control periods first in all patients, also could have affected the results. This point is important, because the open-label phase suggested both a better response with higher doses (500 μg three times daily) and further improvement over time. Thus, the nature of the protocol may have minimised the potential effectiveness of therapy. An Editorial Comment on the design of the study in Gastroenterology noted that the outpatient nature of the trial made compliance a difficult variable to control, but despite the inconclusive results they observed that octreotide represented a useful alternative. These results were combined with the findings of a similar study performed entirely in the U.S. and a number of other smaller studies that had appeared in the literature.

Octreotide is most likely to find its use in a subgroup of patients with AIDS who have secretory processes causing diarrhoea. Additional studies designed to control better for placebo, the effects of food intake, pancreatic function, and assurance of compliance in treatment and stool collections are needed to determine the ultimate benefit of octreotide in patients with AIDS who have diarrhoeal illnesses.

V.III - GASTROINTESTINAL FISTULAE

V.III.I - Disease Characteristics

Gastrointestinal fistulae are abnormal connections between any portion of the gastrointestinal tract and an internal or external epithelial surface. Internal fistulae interconnect hollow viscera or potential spaces, whereas external (enterocutaneous) fistulae connect the gut directly or indirectly to the body surface. Pancreatic fistulae are abnormal communications between the pancreas and the skin (external) or other organs (internal). Pseudocysts may occur following trauma to the pancreas (e.g. during surgery) and they represent a walled off area of necrotic pancreatic tissue and secretions. A pseudocyst may rupture causing ascites or may become infected, leading to the development of an abscess. Biliary fistulae may occur following surgery or trauma to the hepatobiliary tree (e.g. liver transplantation), leading to the leakage of bile either internally or to the skin surface (external). Fistulae in general, and small bowel and pancreatic fistulae in particular, may drain high volumes of fluid, thereby upsetting water/electrolyte balance, in addition to providing a source for recurrent infection. Fistulae are usually managed with a combination of strict skin hygiene and bowel rest (total parenteral nutrition), although high output fistulae may remain patent for weeks or even months. Early fistula closure helps to prevent skin excoriation by pancreatic secretions and reduces the duration of hospital stay, thus decreasing costs.

V.III.II - Rationale for Octreotide Use

Octreotide can decrease fistula output by the inhibition of gastrointestinal hormones, such as. gastrin, cholecystokinin, secretin, motilin. This, in turn, results in decreased secretion of bicarbonate, water, and pancreatic enzymes into the intestine, which was demonstrated in human studies in the late 1980's [24, 25, 26]. Subsequent detailed animal work has shown that octreotide inhibits secretin- and cholecystokinin-stimulated pancreatic amylase secretion in dogs [27] and rats [28,29,30], probably by inhibiting cyclic AMP [31]. In vitro, octreotide also inhibited secretin-stimulated pancreatic protein and fluid secretion in a dose-dependent manner [32], while Nishino and colleagues reported that octreotide inhibited ethanol-induced increases in amylase and CCK secretion [33]. Reduced fistula secretion may also result from decreased intestinal motility and secretion [34] or possibly by a direct effect on mucosal cells [35].

The standard treatment of a fistula includes: identification and localization of the fistula tract, treatment of underlying disease (especially infection), restoration of fluid and electrolyte balance. Most post-operative fistulae close spontaneously with such conservative measures, however for some gut fistulae, bowel rest and total parenteral nutrition (TPN) is necessary. This is a high-cost in hospital approach, that itself is associated with considerable independent morbidity (thrombosis, sepsis). The pharmacological effects of octreotide on gut secretion and motility were therefore attractive to the medical community as a method for speeding fistula healing and reducing hospital stay. Before a clinical development program for octreotide in fistula was designed, the results of retrospective case collections with native somatostatin had become available [36, 37, 38, 39]. As with other indications like GEP tumours, the positive trends toward clinical efficacy with native somatostatin provided further hope to doctors that the enhanced pharmacological profile of octreotide could provide a reliable degree of fistula closure. Small preliminary studies of octreotide involving small numbers of patients were carried out to 'test' the hypothesis that octreotide could reduce fistula output. These demonstrated reduced ileostomy and pancreatic fluid losses.

V.III.III - Clinical Experience with Octreotide

Together with M. Irving, we designed and implemented a prospective, placebo-controlled, double blind randomised trial of octreotide in persistent (despite TPN) pancreatic and enterocutaneous fistula [37]. This study was supposed to recruit 200 patients at 10 centres and last for a 21-day treatment period. The main aim of the study was to discover whether octreotide treatment could decrease fistula closure times more rapidly than TPN alone, while secondary efficacy parameters included reduction in fistula output, reduction in hospital stay, easier fistula management and reduced TPN requirements. In essence this was a surgical outcome study, involving patients who were refractory to available therapy. Also, the patient population was heterogeneous, with both enterocutaneous and pancreatic fistulae included, while patients were recruited from 10 centres each with their own institutional management regime for fistula closure. These design obstacles were to prove crucial to the outcome of the study, as it soon became clear that 200 patients was too high a number to recruit from a practical perspective. Scott et al eventually published the results of the study in 1993 [40]. Only 29 patients with enterocutaneous fistula were recruited, 10 of whom were excluded, which left 8 patients in the placebo arm and 11 patients in the octreotide arm. There was no advantage for octreotide over placebo in the final analysis of data. These results are in contrast to trials conducted in parallel or subsequently. Nubiola et al found that octreotide and TPN led to the closure of enterocutaneous fistulae in 77% of their 27 patients in a mean time of 5.8 days [41]. Octreotide (100 μg s.c. 8-hourly) and TPN resulted in a mean reduction of 55% in fistula output and the most encouraging results were seen in patients with high output fistulas.

In a prospective trial, Tulassay et al reported that octreotide (200 μg/day sc) reduced mean fistula output by 70% after 72 hours of therapy, and spontaneous closure was reported in 14 of 16 patients with high-output postoperative pancreatic fistulae after eight days[42]. Spiliotis and colleagues reported that sc octreotide (300 μg/day) caused a mean reduction of 94% in gastrointestinal fistula output in 32 of 40 patients[43]. Overall, 43% of fistulae closed within 10 days of octreotide therapy, while 70% resolved after one month. Octreotide has also been used successfully in the treatment of pancreatic pseudocysts[44] and biliary fistulae[45]. However, many of these positive studies were affected by the same problems encountered during the clinical development study sponsored by Sandoz. Recruitment and stratification was difficult due to the heterogeneity of aetiology, clinical condition of the patient and management protocols in different hospitals. While well-designed, prospective trials are necessary and desirable if one is to ascertain definitively whether octreotide is of use in fistula treatment, it is unlikely that such studies will ever be performed. The primary reason for this remains the difficulty of performing trials in the surgical/post-operative setting where multiple variables combine to confound recruitment, data collection and standardization procedures.

V.IV - BLEEDING OESOPHAGEAL VARICES

V.IV.I - Disease Characteristics

Portal hypertension secondary to hepatic cirrhosis (due to alcohol or other causes), portal obstruction (e.g. portal vein thrombosis), or infection (schistasomiasis) leads to a diversion of blood away from the liver and towards collateral circulation. From a clinical perspective, the most important collateral vessels in portal hypertension are the thin-walled oesophagogastric junction veins. These vessels engorge to form varices above a portal pressure of 12 mmHg, and larger varices are at significant risk of spontaneous rupture beyond a pressure of 15 mmHg due to increased wall tension. Bleeding from oesophageal varices carries a very poor prognosis, with an estimated mortality of 30-50% following an index bleed[46]. Furthermore, an index bleed from oesophageal varices is a poor prognostic indicator in liver disease, as 60-90% of patients re-bleed within four weeks[47].

V.IV.II - Rationale for Octreotide Use

The scientific basis for developing octreotide as a treatment for variceal bleeding came from preclinical and clinical data garnered from studies of somatostatin in this indication. Somatostatin reduces splanchnic blood flow, thereby decreasing portal venous pressure[48]. Studies of somatostatin showed that it decreased portal pressure to a similar extent to vasopressin, and did not affect systemic haemodynamics when administered as an infusion[49]. Clinical trials with somatostatin in variceal bleeding showed some positive results when compared with established medical therapy such as balloon tamponade and vasopressin. Burroughs et al performed a randomised, double blind, placebo controlled trial of somatostatin and placebo for the treatment of active bleeding and subsequent re-bleeds[50]. Somatostatin was successful in treating variceal bleeds in 64% of cases, compared with 41% placebo patients, while the somatostatin group required significantly fewer blood transfusions. When considering the medical treatment of acute variceal bleeding, both at the time of the inception of the development plan for octreotide and currently in the early 21st century, the main pharmacological alternative remains vasopressin and it's analogues. The posterior pituitary hormone was first used in treating bleeding varices in the late 1950's and early 1960's. It came into common usage despite a lack of hard evidence of it's clinical efficacy, and in a review of 13 controlled trials, Jenkins & Baxter reported that the response to treatment with vasopressin (52%) was similar to the rate of spontaneous resolution of bleeds[51]. The side effects of vasopressin (and analogues such as terlipressin/glypressin) are significant and common. One quarter of patients report adverse events, often cardiovascular in origin, and to this end nitro-glycerine is often added to treatment to prevent serious events. Clinical trials have compared the efficacy and tolerability of somatostatin and vasopressin, with favourable results for somatostatin overall. Saari et al reported that somatostatin controlled bleeding significantly more often than vasopressin (84.4% vs. 57.1%, $p=0.0281$), with less adverse events, but more common rebleeding in the somatostatin group[52]. Mortality was similar in the two groups. Controlled studies have also shown that somatostatin compares relatively favourably with endoscopic sclerotherapy as a primary treatment for bleeding varices. While the efficacy rates between somatostatin and sclerotherapy groups are similar, somatostatin may be associated with a lower incidence of adverse events than sclerotherapy[53,54].

The decision to develop octreotide as a potential therapy in the setting of acute variceal bleeding was based upon a number of points:

1. Mortality in variceal bleeding is huge (30-50% per bleed), and treatment is very costly.
2. Despite the existence of various standard medical treatments, all available therapies were associated with significant weaknesses with respect to efficacy and/or adverse events.
3. The primary treatment for bleeding oesophageal varices was endoscopic injection sclerotherapy, an invasive procedure that requires months/years of training to perfect. Not all hospitals are equipped with an endoscopy unit, and medical therapy had to date failed to provide adequate haemostasis during the "holding period" while a patient was being transferred to a endoscopic unit.
4. Interventional therapies themselves (sclerotherapy, balloon tamponade) were themselves associated with significant side effects.

V.IV.III - Clinical Experience with Octreotide

Following on from the results of clinical and preclinical trials with somatostatin, it was felt that octreotide might have similar or better effects in variceal haemorrhage,

given its more favourable pharmacological profile. Octreotide was shown to reduce splanchnic blood flow in cirrhotic rats[55] and in patients with cirrhosis and portal hypertension[56]. Baxter et al studied the effect of octreotide in nine patients with liver cirrhosis and portal hypertension and found directly recorded intravariceal pressure to be reduced by 38%[57]. At the time that the clinical development program for octreotide in variceal bleeding was being proposed, only one comparative clinical trial had been reported. McKee et al compared octreotide (25μg/h for 48h) with balloon tamponade in the setting of endoscopically proven actively bleeding varices[58]. In both groups of patients, injection sclerotherapy was performed after 48 h. They found that bleeding was well controlled at 4 hours (19/20 with tamponade, and 18/20 with octreotide) and 48 hours (14/20 with tamponade, and 10/20 with octreotide) in both treatment groups. However, patients tolerated octreotide better, as balloon tamponade was associated with discomfort due to pressure effects of the tube. Importantly, survival was significantly higher in the octreotide group compared with patient who underwent balloon tamponade (100% (20/20) vs. 75% (15/20), respectively). On the basis of the result of this trial and the positive preclinical data regarding octreotide (in addition to the positive clinical trials with somatostatin), a clinical trial program was devised in 1987.

Variceal bleeding represents a major consumer of medical resources. Definitive treatment of variceal bleeds is more successful is specialist centres with access to endoscopy than in district hospitals. However, patients often present with variceal bleeds to outlying centres, and an easily administered, well tolerated and effective "holding therapy" is required in the interim period between diagnosis and transportation to a special centre for endoscopic treatment. The existing "holding therapies" consisted of resuscitation, insertion of a Sengstaken-Blakemore tube to control bleeding via tamponade, and/or administration of vasopressin to reduce portal pressure. Both balloon tamponade and vasopressin treatment have been associated with significant adverse events and failure rate. On the basis of the work of McKee et al, in a centre experienced in using tamponade, octreotide demonstrated bleeding control comparable with balloon tamponade, particularly in the first few hours. This indicated that octreotide could be highly beneficial as a short-term measure. The argument that the gold standard of efficacy against placebo had not been tested could be defended as placebo would be unethical in the acutely bleeding patient, and octreotide could be compared with existing treatments and placebo for a few hours while sclerotherapy was being arranged. Octreotide is easily administered intravenously, and requires little or no expertise, is not associated with significant adverse events and does not interfere with later surgical/endoscopic intervention. The ease of administration of octreotide means that it could be given in the hospital or ambulance setting by any staff with basic emergency care training.

On the basis of these points, in addition to the small amount of basic and clinical data, a study of octreotide as a holding therapy in acute variceal bleeding was proposed. No formal comparisons with placebo as a "holding therapy" before sclerotherapy had been made, and similarly the efficacy of octreotide vis-à-vis the main medical treatment, vasopressin, had not been tested. Since the late 1980's/early 1990's, a group of well-controlled, large-scale trials have been published in the literature. The findings of these trials have been clear-cut and have borne out the beliefs of the working group almost in their entirety. The results of these trials are outlined below.

One trial looked at the use of octreotide in the control of post-sclerotherapy bleeding from oesophageal varices (n=42), but also from oesophageal ulcers (n=31) and oesophagitis (n=4)[59]. Patients recruited between 1989 and 1992 received octreotide at a dose of 50 μg/h, but if bleeding was not controlled, hourly boluses of 50 μg were administered for 24 h. The treatment was well tolerated and highly effective (bleeding controlled in 38/42 varices; 30/31 ulcers, 4/4 oesophagitis). In the remaining patient with ulceration, and in 2/4 with varices not controlled with infused octreotide, bleeding was stopped with the addition of bolus doses. The authors concluded that octreotide was a safe and effective treatment for the control of re-bleeding after successful sclerotherapy.

In a study by Sung et al, one hundred patients with bleeding esophageal varices were randomised to receive either octreotide (50 μg i.v. bolus, then 50 μg/hr i.v. infusion for 48 hours) or sclerotherapy[60]. All patients receiving octreotide underwent sclerotherapy after their infusion. There were no significant differences between the groups on the basis of immediate control of bleeding, rebleeding rate, duration of hospital stay, transfusion requirements, while mortality rates at 48 hours, during hospital stay and at 30 days did not differ significantly between the two groups. The authors recommended the use of octreotide in cases where endoscopy was obstructed by heavy bleeding and also in cases where emergency sclerotherapy was unavailable. Besson et al studied the use of sclerotherapy plus octreotide (25 μg/hr, i.v. infusion) versus sclerotherapy plus placebo in a large French randomised, double blind, prospective trial of 199 patients with cirrhosis and variceal bleeding[61]. The primary outcome measure was survival without rebleeding five days after sclerotherapy. The proportion of surviving patients was 85/98 patients (87%) in the octreotide group, which was significantly higher than the placebo group (72/101 patients, 71%; p=0.009). Patients receiving octreotide required transfusions of fewer units of blood than the placebo group (mean 1.2 units, range 0-7 compared with 2.0 units, range 0-10; p=0.006). The odds ratio for treatment failure in the placebo group compared to the octreotide group was 3.3 (95% C.I. 1.5 to 7.3). The mean (±SD) 15-day cumulative survival rate was 88 ± 12% in both groups, and both groups experienced similar and minor side effects. From these data, the authors concluded that the combination of sclerotherapy and octreotide is more effective at controlling acute variceal

bleeding than sclerotherapy alone, but they found no difference in the overall mortality rates in the two approaches. A more recent study by Freitas et al has confirmed these benefits [62]. The effect of iv octreotide on rebleeding rates following endoscopic ligation therapy ("banding") has also been studied. In 100 consecutive patients with endoscopically proven variceal bleeding, Sung et al found that patients who received octreotide (50 μg bolus, 50 μg/h iv infusion for 5 days) during before ligation at endoscopy had a significantly lower rate of rebleeding than patients who underwent ligation alone (9% vs. 38%, respectively; p=0.0007) [63].

Since the early 1990's, groups have also compared octreotide with vasopressin and its analogues. In a randomised trial, Hwang et al reported that iv octreotide (100 μg bolus than 25 μg/hour for 24 hours) controlled bleeding more effectively than vasopressin (0.4U/h) 6 hours after beginning treatment (p=0.03) [64]. At 24 hours, there was a trend in favour of octreotide on the basis of bleeding control (63% vs. 46%), but this was not significant. Mortality rates were similar in both groups, but octreotide was associated with a lower rate of adverse events than vasopressin. In a French multicentre, randomised trial, Silvain et al reported that octreotide (25 μg/hour for 12 hours continuous sc infusion, then 100 μg s.c. at hour 12 and hour 18) and combined terlipressin/nitroglycerin therapy were equally effective in the treatment of acute variceal bleeding in cirrhotic patients [65]. Octreotide was found to be associated with significantly smaller transfusion requirements and side effects than terlipressin/ nitroglycerin. The octreotide group had significantly smaller (p=0.012) transfusion requirements. How do the predictions of the late 1980's measure up to what is known now? From the preclinical standpoint, evidence has accrued that octreotide reduces portal blood flow via alterations in hepatic venous pressure, azygous blood flow and total splanchnic blood flow, although this data is not clear cut. It should be noted that the data regarding the modes of action of native somatostatin and vasopressin remain similarly unclear to this day, despite being available for 2-3 times as long as octreotide. When compared with the mainstream medical therapies of the time, octreotide has proven itself equal in efficacy to balloon tamponade, vasopressin plus nitroglycerin, and terlipressin. The adverse event profile of octreotide in all of these comparative trials has been lower than it's comparator, and in some trials transfusion requirements or even mortality rates have been decreased. No consensus has yet been formed regarding the best first-line medical therapy in variceal bleeding, but in the light of these data, taken in combination with other somatostatin studies [66, 67], a very strong case can be made in favour of octreotide. Our clinical trial program envisaged that octreotide would be best placed to play the role of "holding therapy" while sclerotherapy was being arranged. This role can now be seen as limited in the light of the data published above. Not only could octreotide represent a relevant choice pre-endoscopy, but it also has been shown to decrease the rate of rebleeding from varices post-sclerotherapy/ligation.

A series of meta-analyses of therapies for bleeding oesophageal varices have been published in 2001 and 2002. The most extensive reviews has come from the Cochrane Collaboration, which compared endoscopic sclerotherapy with pharmacotherapy (octreotide, somatostatin, terlipressin, vasopressin) in the management of acute variceal bleeding [68, 69]. The Cochrane Collaboration performs rigorous, highly standardised, regularly updated systematic reviews that judge the efficacy and safety of various therapies, and is the gold standard of what is commonly termed evidence-based medicine. The reviewer group analysed a group of 12 randomised controlled trials, including six with octreotide, and found no difference between endoscopic sclerotherapy and pharmacotherapy in terms of failure to control bleeding, five-day treatment failure, rebleeding before other elective treatments, 42-day rebleeding, mortality before other elective treatments, 42-day mortality, number of blood transfusions, or adverse events. When all pharmacotherapy studies were combined adverse events (including serious adverse events) were more common in the sclerotherapy-treated patient group. It is important to note that when sclerotherapy is compared with pharmacotherapy for the treatment of acute variceal bleeding, the trials are almost invariably performed at busy well-staffed university centres. In contrast, many patients present to regional or district medical units that lack 24-hour expert endoscopist cover. Therefore published direct comparisons between sclerotherapy and pharmacotherapy may not describe accurately the real world scenario where an effective holding therapy is a vital step in maximizing patient survival while transfer to a central endoscopy unit is underway.

Another meta-analysis of the efficacy of the various pharmacotherapies for acute variceal bleeding noted no differences between terlipressin and octreotide [70]. A further meta-analysis examined octreotide in particular, and found that octreotide improved significantly the control of bleeding, and was comparable to sclerotherapy [71]. Overall octreotide had a better adverse event profile than vasopressin/terlipressin and complication rates that were comparable to placebo. The authors highlighted that much of the previous confusion over the clear benefits of octreotide in variceal bleeding resulted from poor study design and difficulties over definitions of rebleeding/control of bleeding.

The role of octreotide in this indication appears to both as a "holding therapy" before definitive treatment can be performed, and also as an adjunct to endoscopy, in the prevention of rebleeding. After many years of debate, current authoritative gastroenterology textbooks have now adopted octreotide as a viable alternative to other pharmacotherapies and as an adjunct to sclerotherapy. One possibility that was raised at the inception of the clinical trials program was that a putative depot preparation of octreotide could be used in the long-term prophylaxis of variceal bleeding in portal hypertensive patients. As octreotide LAR form is now available, what is the future of this possible indication? Initial safety work has been reported, which noted that

octreotide LAR 20mg single dose had no negative impact on renal profiles in cirrhotic hypertensive patients[72]. One trial has been published to date that has looked at the use of octreotide in the prevention of recurrent rebleeds over 6 months[73]. Cirrhotic patients with proven variceal bleeding were programmed to have sclerotherapy alone, or sclerotherapy plus 50 µg octreotide sc twice daily for 6 months. Significantly fewer patients experienced rebleeding while receiving octreotide (1/16) than with sclerotherapy alone (7/16) (p=0.037). Survival was improved, with all five deaths occurring in the sclerotherapy alone group, four from rebleeding. Overall, this improved survival was maintained for 12 months after the end of treatment, but decreased thereafter. The authors concluded that octreotide may represent a viable long-term adjunct to sclerotherapy, and comparison with the efficacy of beta-blockers in this regard would be particularly desirable in light of the development of sustained release somatostatin analogues. Such trials with LAR octreotide may expand the use of octreotide in gastroenterology further.

In summary, gastroenterological societies have now embraced octreotide as a therapeutic option for the treatment of acute variceal bleeding, but only after the results of extensive trials and systematic meta-analytic reviews demonstrated the efficacy and safety of octreotide compared with all available therapies.

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Chapter VI.

Other Clinical Applications of Octreotide

VI.I - INTRODUCTION

As has been noted in previous chapters, somatostatin has a wide range of physiological actions in endocrine and non-endocrine tissues. By necessity the Clinical Development Program for octreotide concentrated on diabetes mellitus, acromegaly and GEP tumours as the main goals of research, and in the latter two indications this ended in registration. Individual clinical groups showed an early interest in collaborating with Sandoz to study the effects of octreotide on gut blood flow, motility and secretion, e.g., variceal bleeding, AIDS-diarrhoea and fistulae. These indications were studied as part of the Clinical Development Program (*Chapter V*). Through our interactions with academic opinion leaders, other potential clinical uses for octreotide were suggested to us, some of which were based on a solid physiological rationale, while others were more theoretical. In general, these clinical entities can be sub-divided into pancreatology, oncology/palliative care medicine and endocrine diseases. Studies were designed, performed and published in multiple conditions during my stewardship of the Clinical Development Program for octreotide. The success of studies into these various potential indications was heterogeneous, with some failing to show efficacy, and others becoming minor - yet important- off-label indications of octreotide today. This chapter traces the scientific rationale and study results of miscellaneous applications of octreotide under the general headings of pancreatic/gastrointestinal disease, oncology/palliative care and pituitary disease.

VI.II - PANCREATIC AND GASTROINTESTINAL DISEASE

VI.II.I - Acute and Chronic Pancreatitis

VI.II.I.I - Disease Characteristics

Pancreatitis is a heterogeneous disease. Many subtypes of pancreatitis exist, each with its own specific aetiological and histopathological pattern, for which there are numerous classification systems. In general, pancreatitis is divided into acute and chronic forms. Acute pancreatitis is a predominantly self-limiting disease that runs a benign course in > 75% of individuals. The commonest causes are acute alcohol ingestion, gallstones and infections. A minority of cases evolves into severe necrotizing pancreatitis, which is associated with systemic shock, organ morbidity and a mortality rate of up to 50%. Damage occurs due to initial destruction of pancreatic and peri-pancreatic tissues, with release of enzymes. Inflammatory cytokines are then liberated and systemic collapse can occur in some individuals. No specific treatment for acute pancreatitis exists, and at the time of the clinical development of octreotide, it was felt that inhibition by octreotide of pancreatic exocrine secretion could reduce the severity of pancreatic damage and reduce morbidity and mortality. Chronic pancreatitis on the other hand is a progressive destructive disease usually due to recurrent acute pancreatitis, chronic alcohol intake, cholelithiasis and anatomical duct distortions. Chronic pancreatitis reduces exocrine and endocrine pancreas function gradually due to inflammation, and fibrosis and calcification become prominent. The precise pathophysiology remains essentially unknown, although duct obstruction and inflammatory cytokines probably play an important role. Chronic pancreatitis is complicated by acute attacks that may require supportive treatment in hospital, or intervention to drain fluid collections, i.e., pancreatic pseudocysts and fistulas. Patients with chronic pancreatitis often suffer from pain, which can require opiate analgesics.
The rationale for using octreotide in the treatment of acute and chronic pancreatitis related to the inhibition of pancreatic exocrine secretion, as 'autodigestion' of the pancreas was held to be a major cause of local and systemic pathology. Also, Limberg and Kommerell reported clinical efficacy of somatostatin-14 in acute pancreatitis in 1980[1], and this was followed by a small number of clinical reports[2,3,4,5,6].

VI.II.I.II - Clinical Experience with Octreotide

VI.II.I.II.I - Acute Pancreatitis

In the latter part of the 1980's independent investigators undertook small clinical trials across Europe, some with financial and logistical support from Sandoz. For instance, in a study of 19 patients with acute pancreatitis, Beechey-

Newman found that patients treated with octreotide (n = 9) experienced significantly less severe disease markers than a placebo group [7]. Patients with mild disease were included, and no difference in mortality rates was noted between the groups. These somewhat positive findings were followed up by other investigators in larger patient groups, and most of these were published in the literature in the mid-1990's. Fiedler et al and Paran et al performed open-label trials in 93 and 38 patients, respectively, that included cases of severe pancreatitis [8,9]. Both trials exhibited significant benefits of octreotide in terms of morbidity. In 2000, Paran et al reported the results of an extension of their original trial and noted again that octreotide was associated with lower morbidity (infection and acute respiratory distress) than a control group [10]. Andriulli et al performed a meta-analysis of trials of octreotide in acute pancreatitis in 1998 [11]. The effect of octreotide on mortality was found to be significant when all trials were assessed together, however, once one open-label trial published in abstract form was removed from the analysis, mortality effects were non-significant. In general, open-label trials demonstrated better effects on complications and mortality than randomised trials. Uhl et al performed a large acute pancreatitis trial that involved 302 patients with an adequate degree of disease severity [12]. No advantage of octreotide (at doses of 100 µg or 200 µg tid) over placebo was noted in terms of complications and mortality. In the era of evidence-based medicine, the negative results of large, well-designed trials outweigh the putative benefits suggested by open-label trials that are published in incomplete form.

VI.II.I.II.II - Chronic Pancreatitis

Chronic pancreatitis is a more complex disease than acute pancreatitis and may be complicated by intractable pain, fluid collections (pseudocysts), bile duct or duodenal obstruction and effusions. Fluid collections can become infected or may impinge on surrounding structures, and surgical drainage is often necessary [13]. As before, octreotide was suggested as a potential treatment for chronic pancreatitis because of its inhibitory effects on exocrine pancreatic secretion. Few clinical trials of octreotide in chronic pancreatitis per se have been performed, although more investigators have examined the utility of octreotide in treating pancreatic pseudocysts. Clinical trials have shown heterogeneous results, and as is the case with acute pancreatitis, one must place greater emphasis on the negative findings of well-designed randomised trials [14], than on positive open label reports [15].

VI.II.I.II.III - Post-ERCP Pancreatitis

Endoscopic retrograde cholangiopancreatography (ERCP) is a widely used diagnostic and therapeutic intervention. ERCP is used to diagnose pancreato-biliary diseases, such as gallstones, pancreatic ampullary tumours and sphincteric strictures. Cutting or biopsy tools can be deployed via the endoscope, which allows treatment at diagnosis in certain conditions. During ERCP, the pancreatic and biliary ducts are cannulated and radio-opaque dye is injected to visualize the ducts under X-ray screening. ERCP can be complicated by post-ERCP pancreatitis, which may develop due to pressure or irritant effects of dye in the pancreatic ducts or because of physical damage during cannulation. The rate of post-ERCP pancreatitis is about 1-5 % after diagnostic endoscopy, and rises to more than double that in cases where pressure measurements or sphincterotomies are made. The spectrum of severity of post-ERCP pancreatitis is wide, with most or all patients exhibiting early asymptomatic hyperamylasemia and in most cases overt pancreatitis is of mild severity. Severe pancreatitis can occur, with its attendant high morbidity and significant mortality.

The inhibitory effect of octreotide on pancreatic enzymes (amylase and lipase), bicarbonate and hormone secretion raised the potential of using octreotide as a pharmacological treatment for ERCP pancreatitis. Animal studies of octreotide had demonstrated its efficacy in reducing histological and biochemical severity of pancreatitis [16,17] and a series of small trials using octreotide as a preventative intervention were completed. The results of these small preliminary trials were mixed, with some showing prevention of post-ERCP pancreatitis, while others showed no effect [18,19,20]. In order to verify whether the preclinical rationale and the early clinical results did indeed indicate any value of octreotide in the prophylaxis of ERCP pancreatitis, formal well-designed trials were planned and implemented. In collaboration with Binmoeller et al in J. Delmont's group at Nice University Hospital, France, we conducted a double blind, placebo controlled comparison of octreotide (100 µg iv before ERCP, then 100 µg s.c. after ERCP) and placebo in the prevention of complications [21]. No significant differences were noted in serum biochemical measures (amylase, lipase) at baseline and 8 and 24 hours after ERCP (*Figure 40*). Similarly, no significant differences were seen between the octreotide and the placebo groups in the rates of pancreatitis and abdominal pain.

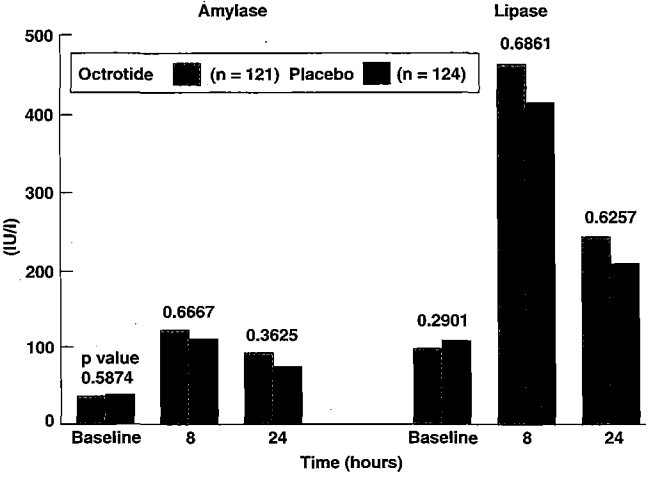

Figure 40. Median serum amylase and lipase activities at baseline and at eight and 24 hours after endoscopic retrograde cholangiopancreatography (ERCP) in octreotide treated (100 µg iv before ERCP, 100 µg sc thereafter) and placebo groups. No significant differences were noted between the octreotide and placebo groups in this study in terms of biochemical or clinical scores ($P > 0.05$) (Adapted from Binmoeller KF, Harris AG, Dumas R, Grimaldi C, Delmont JP [21]).

Subsequently Sternlieb and colleagues terminated a randomised controlled trial after only 84 of the proposed 440 patients had been enrolled[22]. At first glance, the finding that the rate of pancreatitis in octreotide-treated patients was over three times that of placebo-treated patients seemed very surprising. An accompanying editorial, however, noted that the trial used a very liberal definition of pancreatitis, which probably led to a high diagnosis rate in the octreotide group due to post-procedure pain. It is possible that abdominal discomfort, common after beginning octreotide, may have been misinterpreted by the investigators as a clinical symptom of post-ERCP pancreatitis. Furthermore, patients treated with octreotide that underwent sphincterotomy had a lower rate of post-ERCP pancreatitis than those that had no sphincterotomy. This was a very unusual finding, because, as noted above, interventional ERCP is associated with a higher rate of pancreatitis than cannulation procedures. One recent randomised controlled trial was performed by an Italian group in patients at high risk of post-ERCP pancreatitis[23]. Again octreotide was ineffective in preventing pancreatitis and also had no significant effect on post-procedure hyperamylasemia.

In the pre-octreotide era, the pathophysiology of pancreatitis was uncertain and no specific pharmacotherapy existed. On the basis of the above trial results in acute, chronic and post-ERCP pancreatitis, octreotide has not yet been demonstrated to have clinical efficacy. Subsequent prospective trials and meta-analyses, such as those of Andriulli et al, that were performed in recent years have confirmed these negative findings further[11,24,25,26]. The main reason for the failure of the clinical development of octreotide in this condition was the false assumption that the pathophysiology of pancreatitis was caused predominantly by enzymatic secretory processes within the pancreas. Recent advances in inflammation research have uncovered the immunological events that underpin the local and systemic effects of pancreatitis [27,28,29,30]. These mechanisms are complex and involve many levels of cell-cytokine interactions[31]. In this context, the failure of octreotide as monotherapy for reducing acute, chronic and post-ERCP pancreatitis is unsurprising. If anything, the failure of octreotide to influence pancreatitis helped to underline the view that the disease is due to a complex inflammatory immune mechanism, rather than simple 'auto-digestion'. Even today no single pharmacotherapy has shown clear-cut benefit in the prevention and treatment of pancreatitis, and improvements in outcome have been achieved with better disease recognition, and higher quality intensive care management.

VI.II.II - Postoperative Complications of Gastrointestinal Surgery

Following resection or transplantation surgery of the bowel, pancreas or liver, functional disturbances can occur that increase patient morbidity and impact negatively on quality of life. Complications or sequalae of such surgery may occur early, such as fluid collections, fistulae and pancreatic pseudocysts. Alternatively, absorptive or nutritional problems may result later from bowel resection, such as dumping syndrome and short bowel syndrome. The recognised inhibitory effects of octreotide on digestive tract motility, blood flow and secretion meant that individual research groups began using octreotide very soon after its development in an off-label manner to reduce the severity of such post-operative complications of digestive surgery. One of the major problems associated with the study of pharmacotherapies in surgical patients is the wide heterogeneity of the patient population. Two different individuals may be offered similar operations, such as bowel resection, for very different reasons, such as, cancer and inflammatory bowel disease. Similarly, the complexity and physical challenge to the patient of operations on one organ may make it difficult to study the overall effects of a drug, for instance, in pancreatic surgery where outcomes after Whipple's procedure may be analysed together with surgery of lesser severity. With octreotide, initial animal studies and open-label trials in most surgical indications proved positive. However, larger and better-controlled multi-centre trials proved difficult to perform and in some cases were unsuccessful.

VI.II.II.I - Dumping syndrome

VI.II.II.I.I - Disease Characteristics

Dumping syndrome occurs after meals in patients after gastric surgery that have had their pyloric sphincter either resected or functionally deactivated. Patients experience either early or late dumping. Early dumping occurs within 30 minutes of eating a starchy/sugary meal and consists of symptoms of fainting, palpitations and abdominal pain, accompanied by signs such as sweating. Late dumping syndrome occurs 2-3 hours after eating and consists of more severe problems like confusion and loss of consciousness. The aetiology of dumping syndrome remains unclear but early dumping probably results from the body's response to unregulated entry of highly osmotic food into the duodenum. Late dumping has been attributed to vascular and hormonal responses, e.g., insulin secretion, that lead to hypoglycaemia and hypotension.

VI.II.II.I.II - Clinical Experience with Octreotide

Six placebo-controlled trials of octreotide in dumping syndrome were published during my time overseeing the Clinical Development Program for octreotide[32,33,34,35,36,37]. The majority of the studies were short-term carbohydrate meal provocation tests, and almost uniformly octreotide reduced symptoms and cardiovascular/haematological signs of haemodynamic instability. Some patients experienced improvement of pre-existing diarrhoea, while octreotide treatment was associated with the development/worsening of diarrhoea in others. Li-Ling and Irving reviewed the published literature in 2001 and identified seven well-controlled trials[38]. They concluded that administration of octreotide 30 minutes before or immediately after a meal was a pragmatic treatment for dumping syndrome, and octreotide was recommended for treating patients with severe or refractory complaints. Octreotide remains a therapeutic option for dumping syndrome[39].

VI.II.II.II - Short Bowel Syndrome

VI.II.II.II.I - Disease Characteristics

Resection of varying lengths of small intestine may be required for the alleviation of cancer, Crohn's disease, infection or other diseases. Following extensive resection, patients may experience symptoms of malabsorption (including vitamins and minerals) and fluid and electrolyte loss, which is termed short bowel syndrome. The severity of this syndrome is dependent upon the length of remaining intestine. Certain patients, such as those with patients with an intact duodenum and more than two meters of jejunum and an intact colon may be maintained quite successfully on supplemental oral feeds alone. Patients with one to two meters of jejunum and/or partial colonic resection may also require occasional parenteral nutritional 'top-ups'. However, there exists a subset of sufferers with high jejunostomies who are always in a net fluid loss situation. For these patients a normal daily existence is difficult as they are entirely reliant on parenteral nutrition and rehydration and high stoma output can be socially challenging. During the clinical development in other mainstream indications like diabetes and acromegaly, there was great interest from specialists in short bowel syndrome in harnessing the anti-secretory actions of octreotide to reduce the supplemental needs of these patients and therefore improve their quality of life. As before, previous experience with somatostatin in the early 1980's together with findings in other gut indications provided the initial suggestion to us and clinical research groups that octreotide might be efficacious in short bowel syndrome [40]. Trials of octreotide in short bowel syndrome began as early as 1984 and continued throughout the period of my involvement with the clinical development program.

VI.II.II.II.II - Clinical Experience with Octreotide

Studies of octreotide in short bowel syndrome are in general open label, as patient numbers are small. The results of these studies are also difficult to interpret due to the heterogeneity of the patient population. However, most trials demonstrated significant benefits of octreotide in terms of reduced intestinal output. In a review of the subject in 1993, Farthing noted that in short term studies, daily intestinal output was reduced by 16-72 %, while in long-term studies 75-100 % of patients maintained their reduced intestinal output for 4-28 months [41]. In a double-blind trial, Lemann et al found that octreotide (100 µg t.i.d. s.c.) was better than placebo in the reduction of fluid and electrolyte losses ($p<0.001$) in seven patients with high-output jejunostomy after extensive bowel resection (mean residual small bowel length=30 cm) [42]. When compared with a control period, stomal electrolyte output was significantly reduced ($p<0.001$) during octreotide therapy, while bowel transit time was increased significantly ($p<0.01$). In another randomised trial, Kusuhara et al studied the effect of octreotide (100 µg tid sc) on ileostomy output in 12 patients [43]. After a five-day run-in period, patients were randomly assigned to receive either octreotide or placebo for five days, after which they crossed over to the other treatment for five days. Mean daily ileostomy output fell significantly on octreotide ($p<0.05$), while placebo had no effect. Daily sodium and chloride concentrations from dried ileostomy fluid were significantly decreased during the octreotide treatment period. Despite the almost uniformly positive reports regarding octreotide, its role in the treatment of short bowel syndrome remains unclear. Reductions in fluid efflux may decrease parenteral fluid requirements in patients with severe disease, but the magnitudes of these reductions are variable. Furthermore, octreotide is rarely so effective that patients can dramatically curtail or cease parenteral nutrition. In this regard, octreotide will remain an adjunctive, although useful, therapy for short bowel syndrome.

VI.II.III - Complications of Pancreatic Surgery

VI.II.III.I - Disease Characteristics

Major pancreatic surgery, such as Whipple's procedure and resections are associated with significant post-operative complications like pseudocyst, fistula, pancreatic ascites, abscesses and sepsis. A pseudocyst is a walled-off area containing pancreatic secretions, which may form an abscess if infected. Rupture of a pseudocyst may allow the buildup of pancreatic secretions in the peritoneal cavity (pancreatic ascites) or a fistula may form. The mortality rate in major pancreatic surgery is approximately 5 %, while the complication rate can be as high as 20 - 40 %. These complications are caused mainly by leak and build-up of pancreatic exocrine secretions, particularly enzymes. Octreotide is a potent inhibitor of exocrine pancreatic secretion and therefore perioperative administration could reduce the rate of post-operative complications by minimising secretion volumes. Similar to studies in dumping syndrome, short bowel syndrome and other minor potential indications, we interacted with individual research groups to supply octreotide and provide logistical support for data collection and analysis. In the case of pancreatic complications, small studies and individual case reports provided the basis of extensive trials to test the hypothesis that octreotide could reduce postoperative morbidity.

VI.II.III.II - Clinical Experience with Octreotide

Four large multicentre, randomised, placebo-controlled studies have indicated a beneficial role for octreotide in the prevention of post-operative complications of pancreatic surgery. Together with Büchler et al we undertook the first German study, in which 246 patients underwent pancreatic resection for the treatment of chronic pancreatitis (low risk of complications) or pancreatic/periampullary tumours (high risk of complications) [44]. Patients treated perioperatively with octreotide (100 µg t.i.d. s.c.) had a significantly ($p<0.005$) lower rate (32 %) of post-operative complications (pancreatitis, haemorrhage, anastamotic leakage, pancreatic fistula, abscess or pseudocyst formation, renal or pulmonary insufficiency) than patients receiving placebo (55.4%). Octreotide was most effective in reducing post-operative complications in the high-risk tumour group ($p<0.01$). Bassi et al reported a similar multicentre, double blind,

placebo-controlled study performed in Italy, with a patient population of 252 evaluable patients, who were randomised to receive either octreotide (100 μg t.i.d. s.c.) or placebo[45]. Patients were classified as either 'low-risk' (chronic pancreatitis) or 'high-risk' (pancreatic tumours) in a manner similar to the Büchler et al study above, while the post-operative complications assessed were identical in both studies. Again, it was found that the group of patients receiving octreotide perioperatively had a lower rate of post-operative complications than the placebo group (15.6 % and 29.2 %, respectively ($p<0.01$)). However, when each complication was assessed individually, only the rate of pancreatic fistula formation was significantly lowered ($p<0.03$) in patients receiving octreotide, compared with placebo. In contrast to the German study, Bassi et al found that octreotide was more effective in reducing the post-operative complication rate in the 'low-risk' group than in the 'high-risk' group.

Subsequently a second German and a second Italian trial have been performed. The German trial studied only patients requiring surgery due to chronic pancreatitis[46], while the Italian study combined patients with chronic pancreatitis and tumour diagnoses[47]. The second German study found that the complication rate in the octreotide group (16.4 %) was significantly less than the placebo rate (29.6 %; $p = 0.007$). In the second Italian trial, the complication rates were 21.6% and 36.4% in the octreotide and placebo groups, respectively ($p < 0.05$). Significantly more patients in the placebo group suffered from fistulae than in the octreotide group. Berberat et al have reviewed the field in 1999[48] and analysed the results of these four studies and three other large trials, one US (open label, prospective), one French (randomised, double-blind, placebo-controlled), and one Spanish (randomised, double-blind, placebo-controlled). No differences in overall complication rates were seen in the US and Spanish studies, although the latter reported significantly fewer fistulas with octreotide. The French study was similar in size to the German and Italian studies (230 patients) and significantly fewer patients receiving octreotide experienced complications compared with placebo-treated patients. Berberat et al concluded that based on the weight of data from large, well-designed placebo-controlled trials, octreotide can significantly reduce post-operative complications of surgery in those with pancreatic cancer of chronic pancreatitis.

The combined number of patients in the studies outlined above is over 1000, and these patients were assessed, categorised and treated with octreotide in a reproducible manner. Results of the studies taken individually or together demonstrate a clear benefit of octreotide treatment in patients undergoing major pancreatic surgery. The research groups made a conscious effort to define patient risk groups clearly, and endpoints were pragmatic. In this way the flaws encountered in some of the post-ERCP pancreatitis trials (described in an earlier section) were avoided.

VI.II.IV - Chemotherapy-induced Diarrhoea

Studies of patients treated with cytotoxic cancer chemotherapeutics report diarrhoea in about 20% of cases. The aetiology of chemotherapy-induced diarrhoea is complex and may be due to direct toxic effects on DNA in gut cells, in addition to disruption of normal gut absorption and motility. Often, chemotherapy-induced diarrhoea is resistant to treatment with common anti-diarrhoeals, such as, loperamide and other opiates. Initial early experience with octreotide in secretory diarrhoea due to VIPoma and AIDS led oncologists to use octreotide on an investigational basis in refractory chemotherapy diarrhoea. Many case reports and small collections have been published, in addition to modest open-label trials[49, 50, 51]. In general, open label studies demonstrated a response rate of 75 - 95%. However, as with other indications, the positive benefits of uncontrolled studies have not been borne out in controlled trials. Until large-scale comparisons with existing therapy (opiates) are carried out, octreotide will remain an unproven adjunctive therapy for chemotherapy-induced diarrhoea.

VI.III - PITUITARY DISEASE

VI.III.I - TSH-secreting Adenomas

The clinical development of octreotide as a treatment for acromegaly brought the development team at Sandoz into close contact with most major pituitary endocrinology groups in Europe and North America. This collaboration facilitated the use of octreotide in many miscellaneous endocrine conditions, particularly other pituitary tumours, where somatostatin was thought to play a regulatory role. We were able to collect data on the response of patients with TSH-secreting and non-functioning pituitary adenomas. TSH adenomas are rare and aggressive and responded poorly to available surgical and medical treatment, before the advent of octreotide. We collected and analysed data in 52 patients from the largest single series of patients with TSH secreting pituitary adenomas and found that octreotide was safe and effective[52]. The hormonal response (TSH and α-subunit levels) to single doses of octreotide (50 - 100 μg sc) were measured initially and demonstrated falls in the majority of patients (*Figure 41, 42*). In 33 patients studied for short-term (1 - 2 weeks) responses to octreotide (median dose 300 μg daily s.c.), mean (± SD) TSH fell from 14.7 ± 25.9 to 3.8 ± 7.4 mU/l ($p<0.01$). Interestingly, TSH responses improved as treatment progressed over the short term. In approximately three-quarters of patients, thyroid hormone levels were normalised. Following long-term therapy (mean = 20 months), 84 % (21/25) of individuals had normal thyroid hormone levels. During short and long term therapy a minority of individuals experienced escape of thyroid hormone levels, which resolved with dose escalation in some cases. Seven patients experienced tumour shrinkage (30 - 70 %). Three patients developed asymptomatic gallstones during long-term therapy. More recently, a large series from the NIH has been published[53]. This study describes the clinical progress of 25 patients treated at a single centre (in contrast to our multicenter study), however, the therapeutic interventions used were heterogeneous with approximately one third of patients receiving surgery and the rest a combination of various therapies.

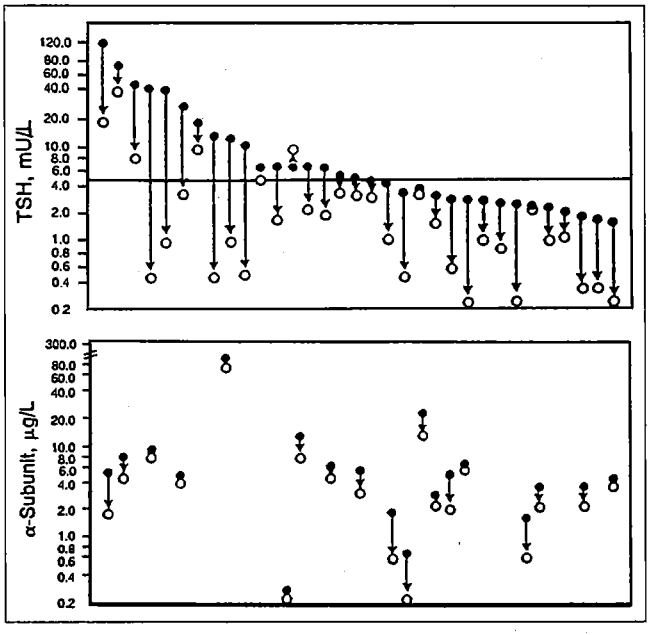

Figure 41. Individual levels of thyroid-stimulating hormone (TSH) and free (-subunit during single-dose octreotide studies (50 - 100 µg sc) in patients with TSH-secreting adenomas. Closed circles denote basal levels and open circles denote nadir levels after 50 - 100 µg octreotide subcutaneously. (Adapted from Chanson P, Weintraub BD, Harris AG[52]).

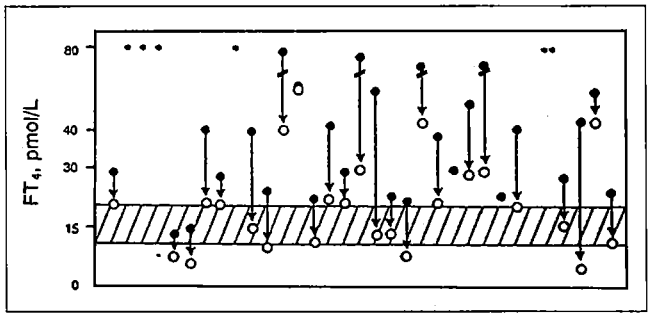

Figure 42. Individual levels of free thyroxine (FT4) during short-term (1 to 2 weeks) octreotide therapy (mean dose 300 µg daily sc) in patients with TSH-secreting adenomas. Closed circles denote basal levels, and open circles denote levels at the end of the short-term study. In patients who also received levothyroxine (indicated by single asterisk) or antithyroid drug (indicated by double asterisk) treatment, interpretation of free T4 (FT4) course was impossible. The horizontal hatched area indicates the normal range for FT4. (Adapted from Chanson P, Weintraub BD, Harris AG[52]).

VI.II.II - Non-functioning Pituitary Adenomas

Similar to the case with acromegaly and TSH pituitary adenomas, we were able to collaborate with academic researchers in neurosurgery and neuroendocrinology to study putative effects of octreotide on non-functioning pituitary adenomas. In 1989, we collaborated with Warnet and Chanson and colleagues to study a series of eight patients with pituitary macroadenomas that had visual disturbance due to chiasmal impingement[54]. In a letter to the New England Journal of Medicine in 1987 this group had reported improvement in visual defects in a patient with a TSH-secreting pituitary adenoma treated with octreotide[55]. Our eight patients included two with non-functioning adenomas, two with TSH-secreting adenomas, two with gonadotropin-secreting adenomas, one with a silent ACTH-secreting adenoma and one with acromegaly. The patients with gonadotropin-secreting adenomas were unresponsive to octreotide, which was instituted at a dose of 100 µg/day via sc infusion. The six other patients experienced rapid (within hours to days) and prolonged visual field/acuity improvements (*Figure 43*). These changes were not accompanied by demonstrable changes in tumour size in five of six patients. The rapidity of improvements in some of the patients suggested to us that somatostatin agonism could have direct visual effects via the optic nerve or the retina. De Bruin at al used[111] In-octreotide scintigraphy to demonstrate the presence of somatostatin receptors on six of seven postoperatively-confirmed non-functioning pituitary adenomas. Three of four somatostatin receptor positive patients that received 1200 µg octreotide s.c. daily experiencedvisual field improvement, despite a lack of objective improvements on CT scanning[56].
Working subsequently with Warnet et al, we reported the results of the French Multicenter study looking at the effects of octreotide on opthalmological and surgical outcomes

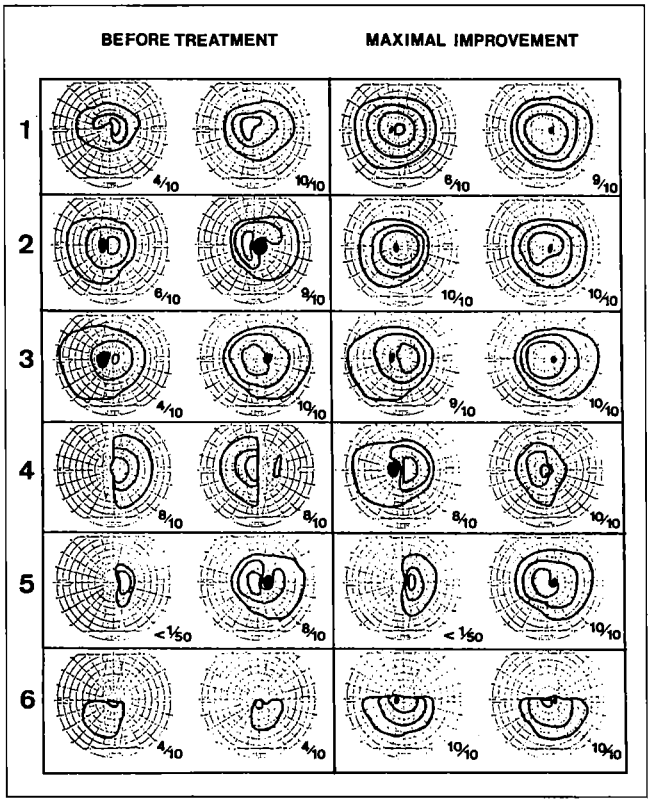

Figure 43. Visual acuity and visual fields before (left) and during (right) octreotide treatment in six patients with pituitary macroadenoma. Visual fields were plotted using a Goldmann perimeter with a 64-sq mm object at 1-candela/sq m light intensity (outer plot) and with 4- and 1-sq mm objects at 0.315 candela per square metre of light intensity (inner plots). (Adapted from A Warnet, E Lajeunie, F Gelbert, M Duet, SN Diop, P Chanson, J Cophignon, AG Harris[54])

only in patients with non-functioning adenomas [57]. The patient population was heterogeneous, unlike the TSH adenoma group described above. Of 24 patients, 22 had non-functioning adenomas that were immunohistochemically positive for ACTH (n=2), gonadotropin (n=7), (-subunit (n=1), GH (n=1) or negative (n=4). Nine others had no tumour staining performed. Doses of octreotide varied from 100-600 μg/day and total octreotide treatment time varied greatly from as short as one day to as long as 700 days. The data collected in this study did not demonstrate clear-cut benefits of octreotide treatment perioperatively. Some benefits in terms of visual fields were noted, but response to treatment was difficult to predict, and a small number of patients experienced worsening of visual function. As in the smaller study above, tumour shrinkage did not accompany or predict improvements in visual fields or acuity. We suggested that improvements in visual function associated with octreotide might be mediated via vascular effects at the level of the tumour and/or chiasma or via direct somatostatinergic neuronal actions. In conclusion, some patients with large non-functioning pituitary macroadenomas accompanied by visual disturbance may experience rapid and prolonged improvement in visual function during octreotide therapy. These improvements are not explained by tumour shrinkage alone, as this occurred in a minority of patients. Those who respond rapidly to octreotide may benefit from longer-term treatment and the judgement regarding the urgency/timing of neurosurgery in such patients should take these effects into account.

VI.III.III - Tall Stature

Treatment of tall and short stature in endocrinologically normal children has always been an area of great controversy. Previous interventions like oestrogen (for girls) and testosterone (for boys) were associated with unwanted hormonal side effects. The use of a somatostatin analogue to modulate growth spurts via precisely targeted GH axis inhibition was therefore attractive. We conducted a small study of octreotide with Tauber et al in French adolescents with constitutionally tall stature (>2 SD above chronological age and a predicted height of >180 cm for girls and >190 cm for boys) [58]. The response to octreotide was generally rapid, although great inter-individual variability existed. Although final height had not been reached by the end of the study, a mean reduction of 4.9 cm was achieved, which was considered modest (*Table 11*). One patient had asymptomatic microlithiasis, which disappeared after ursodeoxycholic acid therapy and remained normal after octreotide was discontinued. Our results were followed in 1995 in a British study of nine tall children who received continuous octreotide infusions at night for two years [59]. Median reductions in height were again modest (3.5 cm), and the authors suggested that prepubertal height could be blunted with octreotide, thereby reducing the baseline height from which the growth spurt would begin. No effect on thyroid secretion was noted.

	Before SMS 201-995			6 months			12 months		
Patients	ΔSDS/BA GR	Number of GH pulses	SmC U/ml	ΔSDS/BA GR	Number of GH pulses	SmC U/ml	ΔSDS/BA GR	Number of GH pulses	SmC U/ml
1	−0.6	6	1.6	−2.2	1	1.1	−0.4	2	1.0
2	+0.2	3	1.4	−1.5	2	0.6	–	–	–
3	+0.3	13	1.7	0.6	3	2	−1.7	3	0.7
4	+0.4	8	1.6	−2.5	5	0.6	−0.4	4	1.4
5	+0.9	8	2.8	−2.9	2	1	−1.4	6	0.4
6	+0.5	9	1.3	−3.4	5	1.1	−2.2	3	1.4
7	+0.7	6	1.7	−1.7	4	1.3	0	4	1.0
8	+0.2	8	–	−3.3	3	–	–	–	–
9	+0.1	6	–	0	8	–	–	–	–
10	−0.6	8	–	−2.2	3	–	–	–	–
Mean	+0.4	7.5*	1.7	−2.0	3.6*	1.1*	−1.0	3.7	1.0*
SD	0.2	2.6	0.5	1.1	2	0.5	0.9	3.4	0.4

*$p<0.01$.

Table 11. Evolution of growth rate (GR), number of growth hormone (GH) pulses during 24 hours and IGF-1 (SmC) before and after 6 and 12 months of octreotide therapy. Octreotide therapy reduced significantly both the number of GH pulses and mean IGF-1 level, while the growth rate (estimated as rate of change of stature relative to basal height) was slowed modestly (Adapted from Tauber JP, Vigoni F, Harris AG, Rochicchioli P [58]).

VI.IV - ANALGESIC EFFECTS OF OCTREOTIDE

Somatostatin receptors are found throughout the central and peripheral nervous systems and the immune system. A neuroimmune regulatory circuit of somatostatin and substance P has been suggested to be involved in the modulation of joint inflammation (and pain) in patients with rheumatoid arthritis [60]. Somatostatin may inhibit the transmission of nociceptive stimuli through its inhibitory effect on substance P release. In the rat brain, octreotide binds to opiate receptors with an affinity about 200 times higher than somatostatin and octreotide may mediate analgesic effects via interactions with opiate receptors in the brain and spinal cord [61]. Clinical studies in pain syndromes like fibromyalgia have shown no effect of octreotide [62], although the complex psychopathology and deconditioning associated with this disease has confounded analgesic pharmacotherapy. However, octreotide has recently been shown to be a substrate of the transporter protein p-glycoprotein [63,64]. P-glycoprotein acts as a protectant against exogenous toxins/xenobiotics and is expressed in high concentrations in the small intestine, kidney, liver and blood-brain barrier. At the blood-brain barrier, p-glycoprotein limits the access of many drugs to privileged sites within the brain. As such, p-glycoprotein may prevent adequate access of octreotide to receptors within the central nervous system in the clinical setting, thus limiting potential somatostatinergic analgesic effects. Combination therapy with octreotide and a p-glycoprotein antagonist might represent a future mechanism for delivering therapeutic octreotide doses into the brain.

In cancer-related pain, intrathecal octreotide has been very effective in a small number of patients with terminal cancer. Penn et al reported that pain relief and a reduction in opiate requirements were achieved with an intrathecal octreotide infusion in six patients with terminal intractable neuropathic pain [65,66]. The efficacy and safety of high doses of octreotide (3 mg/day) as analgesia in cancer pain has been reported in small studies both during the Clinical Development Program [67] and subsequently [68]. Together with Schmidt and colleagues we studied the effect of octreotide as an analgesic in two acromegalics patients with intractable headache [69]. This study was performed double blind, with the patients receiving octreotide 100 µg or placebo in a series of 15 hospital visits. Pain was rated on a visual analogue scale. We found that the patients experienced nearly complete pain relief 4 - 15 minutes after octreotide injection. The pain control was long lasting with a duration of action of 2 - 8.5 hours (*Figure 44*). Both patients had been receiving multiple analgesic drugs pre-octreotide, and once regular octreotide therapy was instituted, these requirements fell dramatically. Analgesia was not mediated by opiate receptors, as naloxone injection failed to block the activity of octreotide in both patients. Withdrawal of octreotide or dose-reduction resulted in return of headaches, and both patients remained stable on therapy 71-82 months after beginning octreotide treatment. We also screened 11 patients with chronic pain of various aetiologies and found that a minority (3/11) reported improvements, however, these were not studied in a double-blind manner. It is difficult to extrapolate the effects of octreotide on headache in acromegalic patients to general analgesic activity in heterogeneous groups of patients with serious intractable pain. Given the difficulty and ethical issues surrounding pain trials in cancer patients, octreotide is likely to remain an adjunctive therapy for palliative care specialists treating severe opiate resistant pain.

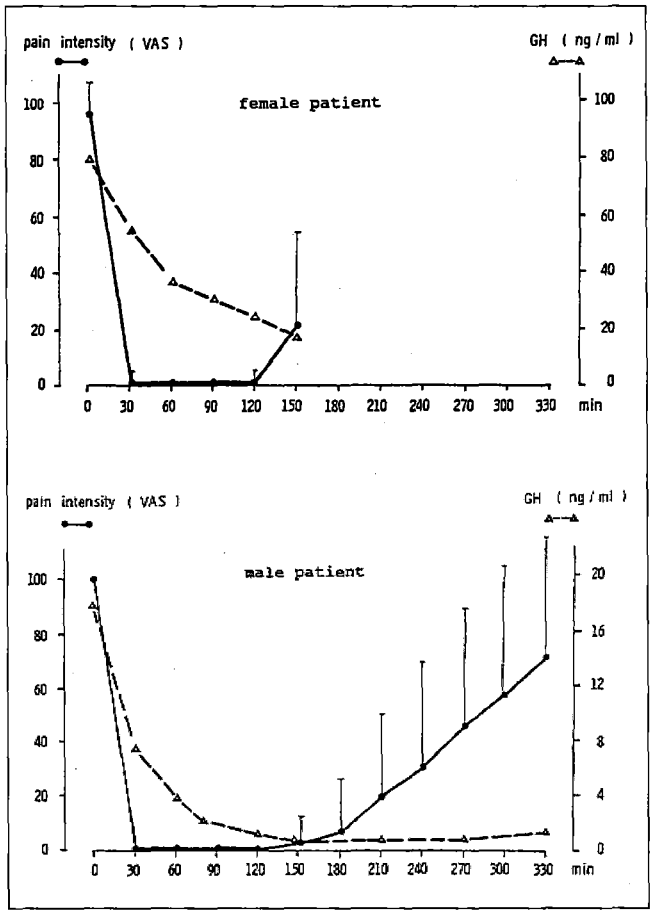

Figure 44. Growth hormone (GH) levels and average pain intensity (VAS) after sc injection of octreotide. Patients were given 100 µg of octreotide at 0 min and 100 g of glucose orally at 30 min. △ = GH level, ● = pain intensity (mean and S.D.). (Adapted from K Schmidt, PH Althoff, AG Harris, H Prestele, PM Schumm-Draeger, KH Usadel [69]).

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Chapter VII.

Safety Issues with Octreotide during the Clinical Development Program

Most side effects associated with octreotide administration are either local or gastrointestinal.

VII.I - LOCAL REACTIONS

Local reactions include pain, a sensation of stinging, tingling or burning at the site of injection, with redness and swelling. These reactions rarely last more than 15 minutes. We found that local discomfort may be reduced by allowing the solution to reach room temperature before injection or by injecting a smaller volume using a more concentrated solution.

VII.II - GENERAL GASTROINTESTINAL ADVERSE EVENTS

Gastrointestinal side effects include anorexia, nausea, vomiting, cramp-like abdominal pain, abdominal bloating, flatulence, loose stools, diarrhoea and steatorrhea. Avoiding meals around the time of injection may reduce these side effects. In rare instances, gastrointestinal side effects may resemble acute intestinal obstruction with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding.

VII.III - PANCREATIC FUNCTION

Impairment of pancreatic function was not a significant problem during acute and long-term octreotide administration in normal volunteers and acromegalic patients[1,2,3]. Exocrine and endocrine pancreatic functions were evaluated by non-invasive means (faecal fat excretion, mouth-to-caecum transit time, Lundh meal, hormonal profiling). Octreotide (200-400 μg/day for up to 30 months) significantly increased average faecal fat excretion compared with the off treatment level (12.9 versus 1.9 g/day, $p<0.05$). Three of five patients reported an increased bowel frequency indicating possible steatorrhoea and in two others this was transient. Although measured faecal fat excretion increases, there is no evidence that long-term treatment with octreotide leads to significant diminution of pancreatic function and nutritional deficiency due to malabsorption[4,5,6,7].
A case of acute pancreatitis was reported in an acromegalic man taking octreotide. However, the causal relationship of acute pancreatitis to octreotide therapy has been questioned, as cholelithiasis cannot be excluded on the basis of a single ultrasound scan[8]. Moreover, computed tomography (CT) and ERCP had not been performed in this patient.

VII.IV - HEPATOBILIARY ADVERSE EVENTS

VII.IV.I - Hepatic Adverse Events

Isolated cases of hepatic and biliary dysfunction in patients on octreotide have been reported[9]. Acute noncholestatic hepatitis followed by normalization of transaminase values on withdrawal of octreotide has been reported in some cases. Administration of octreotide can produce hyperbilirubinaemia associated with elevations of alkaline phosphatase, gamma-glutamyl transpsptidase and, to a lesser extent, transaminases. Cases of biliary colic on abrupt withdrawal of octreotide have been reported[10]. While the attacks can be severe, they were short-lived with no apparent sequelae. It is possible that rebound gallbladder hypercontractility is the cause of biliary colic on abrupt cessation of octreotide. Rhodes et al have suggested that patients on long-term octreotide therapy may benefit from a drug-free period each week to enable evacuation of the contents of the gallbladder and reduce the risk of gallstone formation[11].
When the first reports of gallstones occurring in patients treated with octreotide appeared, we implemented a cogent program with leading academic centres in France, the United Kingdom, The Netherlands and Germany to unravel the pathogenesis of octreotide-induced gallstones. This pro-

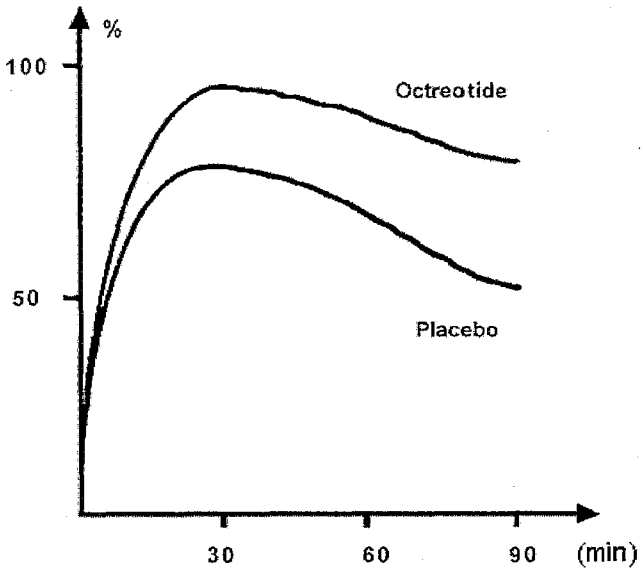

Figure 45. Peak liver radioactivity as assessed by technetium scanning is higher at 35 min in the octreotide treated subjects compared to the placebo groups (29 min) (P = 0.07) (Adapted from C Grimaldi, J Darcourt, AG Harris, E Lebot, F Lapalus, J Delmont[13]).

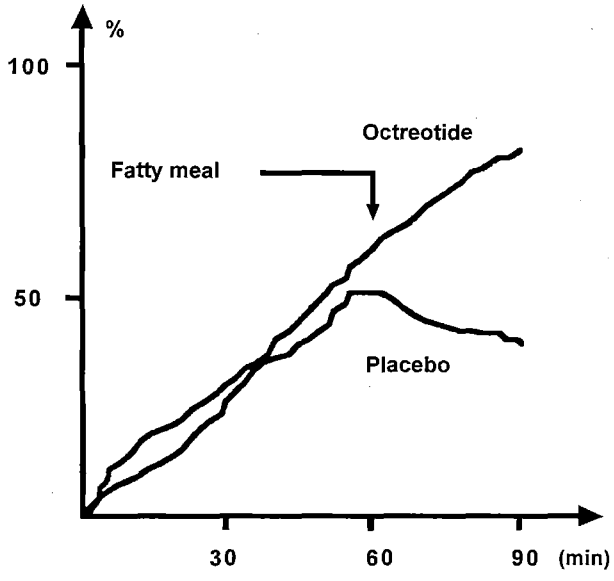

Figure 46. Peak gallbladder radioactivity was significantly delayed (P = 0.03) in the octreotide group (t_{max} = 90 min) compared to the placebo group (t_{max} = 68 min). (Adapted from C Grimaldi, J Darcourt, AG Harris, E Lebot, F Lapalus, J Delmont[13]).

		Normals	Acromegalic patients: acute effect of octreotide	
	Units	(N = 14)	Before	2 hr after
$t_{max\ (L)}$	min	5-15	9.4 ± 0.6	14.0 ± 1.7[a*]
$t_{1/2\ (L)}$	min	30-50	39.3 ± 5.0	53.3 ± 5.0[a]
$L_{120\ min}$	%	<10	9.8 ± 1.0	20.9 ± 3.1[b]
$t_{dis\ (L)}$	min	<60	58.6 ± 1.5	85.7 ± 7.2[b]
t_G	min	10-30	20.3 ± 3.0	23.4 ± 2.4
$t_{max\ (G)}$	min	30-60	43.1 ± 6.3	110.0 ± 6.5[c]
$t_{rad\ (D)}$	min	<60	31.5 ± 5.0	>120

Table 12. Dynamics of bile excretion in 14 normal adults and acute effect of octreotide in 7 untreated acromegalic patients compared with values before injection of 5 _g octreotide:
[a] = p < 0.05; [b] = p < 0.005; [c] = p < 0.001.

t_{max}: maximum liver (L) radioactivity
$t_{1/2\ (L)}$: 50% of maximum liver radioactivity
L_{120}: remaining radioactivity in the liver at 120 minutes
$t_{dis\ (L)}$: disappearance of liver radioactivity
t_G: time at which gallbladder was visualized
$t_{max(G)}$: Peak gallbladder radioactivity
$t_{rad\ (D)}$: radioactivity in duodenum

(Adapted from Zhu XF et al.[16]).

		Acromegalic patients: acute effect of octreotide	Acromegalic patients: long-term and post withdrawal effects of octreotide	
	Units	Before OCT	During OCT	After withdrawal
$t_{max\ (L)}$	min	9.4 ± 0.6	9.2 ± 0.8	9.5 ± 0.9
$t_{1/2\ (L)}$	min	39.0 ± 3.0	40.0 ± 5.8	30.0 ± 1.3
$L_{120\ min}$	%	9.8 ± 1.0	15.2 ± 4.0	11.2 ± 2.5
$t_{dis\ (L)}$	min	58.5 ± 1.5	75.0 ± 11.2	61.7 ± 3.9
t_G	min	20.3 ± 3.0	40.0 ± 15.8	16.7 ± 3.3
$t_{max\ (G)}$	min	43.1 ± 6.1	103.3 ± 7.9 †	51.7 ± 6.9 ‡
$t_{rad\ (D)}$	min	31.7 ± 5.0	63.3 ± 17.1	36.7 ± 7.9

Table 13. Dynamics of bile excretion during long-term octreotide (oct) treatment (500 ± 100 (/day) and after discontinuation of therapy in 6 acromegalic patients. EHIDA imaging was repeated approximately two weeks after cessation of therapy, when gallbladder contractility had normalized as assessed by fat meal test in all six patients. † Compared with values of untreated patients, P < 0.001. ‡Compared with values during long-term treatment, P < 0.001.
(Adapted from Zhu XF et al.[16]).

	PRGC (%)						
Patients	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Mean ± SEM
Before treatment	70.3	81.3	83.3	90.5	77.5	72.4	79.2 ± 2.4
End of treatment	6.6	34.2	2.5	2.8	14.1	5.4	10.9 ± 5.0†
After 1 week	89.8	84.4	64.3	95.7	40.6	43.8	69.7 ± 10.1
After 2 weeks	94.6	84.3	95.1	90.5	65.4	69.3	83.2 ± 4.6*

Table 14. The restoration of percentage relative gallbladder contractility (PRGC) in six acromegalic patients after cessation of octreotide treatment. Pt = patient. Comparison with value at end of treatment: *p<0.001; †p<0.001. (Adapted from Shi YF et al[18]).

gram focussed on studying the composition of bile and gallstones associated with octreotide therapy and establishing the prevalence and incidence of octreotide-associated gallstones.

VII.IV.II - Gallstones

VII.IV.II.I - Background Research

The aetiology of gallstones is complex and multifactorial, involving concentration of ions, pigments, cholesterol, water and gallbladder motility amongst others. The effect of octreotide (1 μg sc tid) on gallbladder bile composition was investigated in 10 prairie dogs in comparison to 14 control animals receiving normal saline [12]. Octreotide increased hepatic bile concentrations of bilirubin monoglucuronide, total bilirubin and total protein. Gallbladder stasis, bile calcium, bilirubin monoglucuronide, total bilirubin, total protein, and total lipids were increased in the octreotide group. Animals receiving octreotide decreased hepatic and gallbladder bile pH. No differences in cholesterol saturation index were observed. These alterations in gallbladder bile composition may increase the likelihood of cholesterol and calcium bilirubinate precipitation, which may explain the increased incidence of gallstone formation during chronic octreotide therapy.

Healthy Volunteer Studies

In a double blind randomized placebo controlled study with Grimaldi and Delmont et al at Nice University, we investigated, using cholescintigraphy, the effect of octreotide (100 μg iv) on hepatic bile secretion and gallbladder emptying in 12 healthy volunteers. While there was no significant difference between the time to peak ^{99} Tc-PBIDA activity in the octreotide and the placebo group, the ratio of gallbladder activity at 90 minutes to the activity at 60 minutes was significantly higher in the octreotide group (1.53) than in the placebo group (0.95) ($p<0.01$). Thus, the delayed release of ^{99} Tc-PBIDA from the livers of the octreotide treated subjects after a fatty meal probably reflected a decrease in bile secretion, which occurred in conjunction with the inhibition of gallbladder contraction (*Figures 45, 46*) [13].

VII.IV.II.II - Studies in Acromegalic Patients

We have shown with Erlinger et al in Paris that octreotide treatment may induce the formation of cholesterol crystals but does not increase the cholesterol saturation index [14]. Thirteen patients with active acromegaly took part in the study. Each patient received octreotide (100 μg t.i.d. s.c) for a three-month study period, after which 12 patients continued with octreotide therapy. Fasting gallbladder bile was sampled during upper gastrointestinal endoscopy after stimulation with ceruletide. Bile was studied before and the end of treatment (n=7), only before treatment (n=4), or only at the end of treatment (n=2). Prior to octreotide treatment the bile of 10 of 11 patients was supersaturated with cholesterol, although cholesterol crystals could not be detected on microscopic examination. At the end of the treatment period 7 of 9 bile samples were supersaturated with cholesterol and cholesterol crystals were detected in three samples. There was no significant difference in relative proportions of bile acids, cholesterol and phospholipids before and after treatment. Gallstones were detected on follow-up ultrasonography of four patients, including three who had already developed cholesterol crystals. We concluded that octreotide impairs gallbladder motility and/or decreases cholesterol nucleation time.

With Buscail et al in Toulouse we studied the risk of gallstone formation during long-term treatment with continuous subcutaneous infusion of octreotide (mean duration 26.5 months, mean dose 541 μg/day) in 12 patients with acromegaly [15]. Bile was collected by duodenal intubation and abdominal ultrasound/cholecystograms were performed before, during, and 45 days after octreotide treatment. Cholesterol crystals were present in 58.3% of patients during treatment, compared with only 3% before octreotide treatment. Twenty-five percent of patients had cholesterol microcrystals 45 days after discontinuing octreotide. In three patients treated with octreotide for more than six months, cholesterol crystals preceded the appearance of radiolucent gallstones. One of these patients underwent cholecystectomy because of biliary colic, while gallstones dissolved completely after 10 months of ursodeoxycholic acid treatment in combination with maintenance octreotide therapy.

In a study we conducted with Zhu and Shi's group in Beijing, China, percentage relative gallbladder contraction (PRGC) was measured 6 hours after small doses (5 and 12.5 μg) of octreotide, and was found to be significantly lower than pre-treatment levels (28.8 ± 7.4 %, $p<0.001$) [16]. Ten hours after administration of 5 μg and 12.5 μg doses of octreotide, PRGC levels returned to pre-treatment levels. We concluded that owing to the significant inhibition of gallbladder contractility at doses as low as 5 μg, the lowering of octreotide doses in long-term therapy might not be effective in preventing gallbladder dysfunction. In another [99mTc] EHIDA study we conducted with Zhu et al [17], PGRC was also inhibited by single doses of octreotide in acromegalic patients compared with a matched group of healthy controls. When this study assessed the long-term effects of octreotide on gallbladder function, we found that after cessation of octreotide therapy for two weeks, gallbladder function had returned to baseline, indicating that the effects of octreotide on biliary function were relatively short-lived (*Tables 12, 13*).

With Shi et al we also reported that withdrawal of octreotide therapy in 6 Chinese acromegalic patients who did not develop gallstones during long-term octreotide therapy (500 ± 245 μg/day for 16.3 ± 7.6 months) was associated with a return of gallbladder contractility within one week (*Table 14*) [18]. Of the eight acromegalic patients who developed gallstones during chronic octreotide therapy (1020 ± 554 μg/day for 32.6 ± 11.5 months), four normalized their gallbladder contractility within two weeks after cessation of octreotide. Gallbladder contractility improved without returning to normal six months after withdrawal of octreotide in the other three patients and was found to be normal five months after discontinuation in the fourth patient.

In 1992, Hopman et al reported that in a group of 5 acromegalics, compared with eight normal control subjects, octreotide (100 μg twice/thrice daily sc for 6-32 months) reduced (-125 ± 194 cm^3 at 120 min,) significantly the integrated post-prandial gallbladder contraction 45 minutes after administration of the final 100 μg dose [19]. Octreotide had no effect on basal levels of cholecystokinin (CCK) 45 minutes and eight hours after injection. Postprandial CCK elevations, 45 minutes and eight hours after octreotide administration, were significantly lower than CCK levels measured two weeks after withdrawal of octreotide ($p<0.05$). Hopman et al also assayed plasma pancreatic polypeptide levels after the ingestion of a standard meal and found that integrated post-prandial rises were inhibited during a period of 45 minutes after octreotide injection (0.1 ± 0.2 nmol/l at 120 min), but inhibition diminished eight hours and two weeks after administration (3.0 ± 1.0 nmol/l at 120 min and 106 ± 1.6 nmol/l at 120 min, respectively, $p<0.05$). The authors concluded that the inhibition of CCK and pancreatic polypeptide-mediated systems was not involved in the reduction in postprandial gallbladder contraction in acromegalic patients receiving octreotide.

Bigg-Wither found no significant difference found between the rates of gallstone development in 15 acromegalic and 10 obstructive sleep apnoea syndrome (OSAS) patients during octreotide treatment (100-500 μg three times per day sc, 4-32 months duration in acromegalics and 100 μg twice daily sc, 2-3 months duration in OSAS patients), although an increased risk of cholelithiasis was associated with octreotide therapy in both groups [20]. In the six of the 15 acromegalics and in two of the 10 OSAS patients who developed gallstones, a wide variation in the concentration of gallstones in the gallbladder was reported (from "a few" to "packed'). Gallbladder volume was significantly increased in all individuals, more markedly in acromegalic patients (from 27 ± 3 ml to 71 ± 8 mL, $p=0.0002$ and from 30 ± 4 mL to 50 ± 6 mL, $p=0.0006$, in acromegalic and OSAS groups, respectively). Eight months after withdrawal of octreotide, it was found that gallstones had resolved spontaneously in seven of eight patients after octreotide therapy. It was concluded that octreotide was associated with increased risk of gallstone formation, possibly due to increases in gallbladder volume, presumably caused by the inhibition of contraction and emptying, which resolved after the termination of octreotide treatment.

Catnach el al stated that fasting gallbladder volume had little effect on the development of gallstones in acromegalic patients receiving octreotide [21]. They disagreed with the conclusion of Bigg-Wither et al above that increased gallbladder volume was possibly linked to cholelithiasis. The authors highlighted studies in which increased gallbladder volume was not associated with a parallel rise in the risk of gallstone formation. Catnach and colleagues also pointed out that the gallbladders of acromegalics not undergoing octreotide therapy have been found to be three times larger than normal, with no associated increase in reported incidence of cholelithiasis. Catnach et al noted the increase in biliary cholesterol concentrations seen in acromegalic and normal patients with octreotide and identified octreotide as being a likely culprit for the increased risk of gallstone formation during therapy.

The studies performed during the Clinical Development Program indicated that incidence of gallstones in octreotide-treated patients is greater than that of age-, sex- and weight-matched controls. We performed these studies in acromegalic patients because of the consistent availability of pre-treatment gallbladder ultrasonography. It should be noted, however, that acromegalic patients could have a greater risk of gallstones because of their inherent gallbladder hypomotility as reported by Catnach et al above [21]. Thus the incidence of gallstones in patients treated with octreotide for other disorders may be lower. Dowling and colleagues investigated the mechanisms of gallstone formation during long-term octreotide therapy (*see Figures 47, 48*) and expanded the understanding of cholelithiasis by using octreotide-induced gallstones as a human in vivo disease model. These studies [22, 23, 24] demonstrated that most octreotide-associated gallstones are cholesterol-rich, probably stemming from cholesterol-supersaturated bile, and a high molar ratio of cholesterol to phospholipids in the vesicular biliary fraction. These features are also associated with rapid nucleation of cholesterol microcrystals and a doubling of deoxycholic acid concentration independent of gallstone formation. In addition to abnormalities in biliary composition, octreotide also had been shown to impair emptying of the gallbladder [1], with the principal mechanism for this being inhibition of cholecystokinin secretion [25, 26]. Therefore, the pathogenesis of octreotide-induced gallstones consists of multiple defects, the first of these being the production of supersaturated bile with a cholesterol saturation index >1. Secondly, there is a nucleation defect, which consists of an imbalance between the promoters and inhibitors of cholesterol microcrystal formation that facilitates the development of microcrystals in supersaturated bile. Thirdly, the development of gallstones is enhanced by gallbladder stasis secondary to the inhibition of meal-stimulated cholecystokinin release from the intestinal wall. Gallbladder hypomotility promotes stagnation of bile and enhances the ability of excess surface mucus to capture cholesterol microcrystals. To these direct biliary effects must be added the impact of octreotide-induced impairment of small and large intestinal motility, which disrupts normal patterns of reabsorption of water and biliary components [27]. There are few studies of gallstone composition in patients developing stones during octreotide treatment. Initial reports suggest that octreotide-associated gallstones are radiolucent, cholesterol-rich and dissolve with oral ursochenodeoxycholic acid treatment [28]. It has been suggested that gallstones in these patients might be prevented during octreotide therapy by administration of either cholecystokinin, non-steroidal anti-inflammatory agents or other anticholic agents. Cisapride does not reverse the effects of octreotide on the gallbladder but it can increase small and large bowel transit times [29], which may impact biliary composition [30]. Intra-hepatic cholelithiasis is also a potential problem -albeit a rare one- in patients with acromegaly undergoing octreotide therapy that are pre-disposed to slow intra-hepatic biliary flow [31].

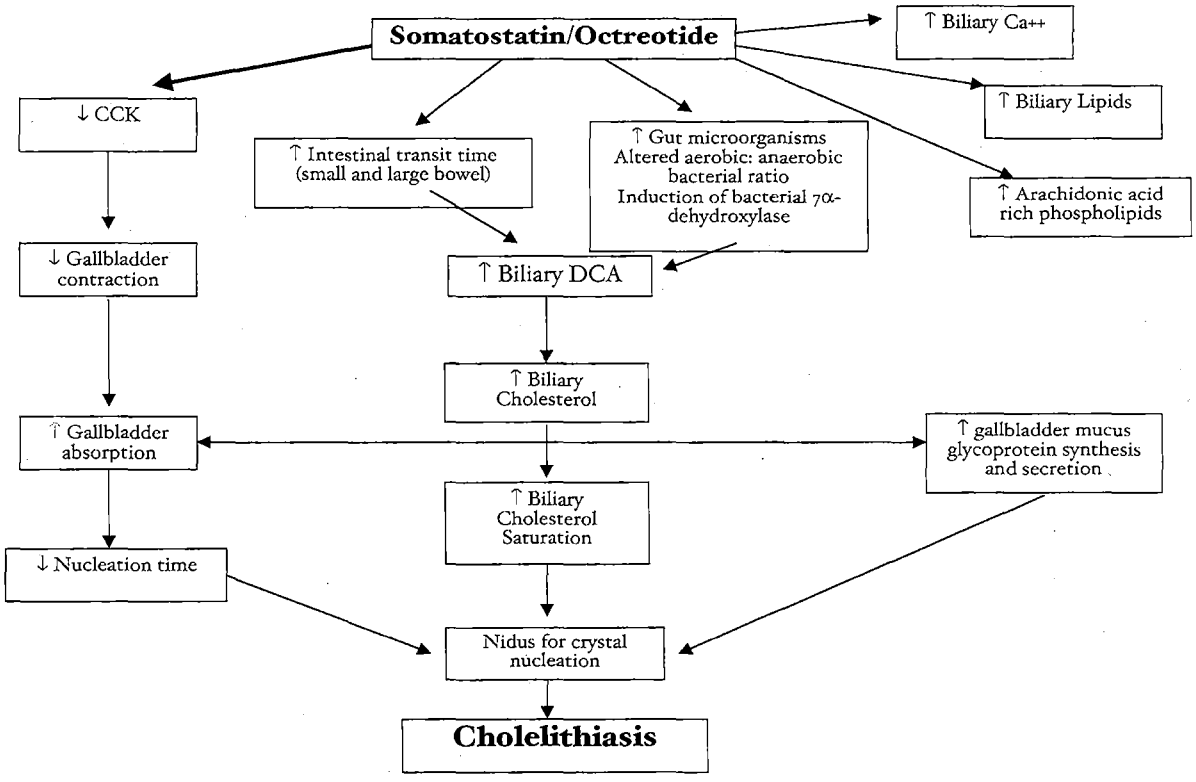

Figure 47. Model for somatostatin/octreotide-induced gallstone formation. CCK = cholecystokinin, DCA = deoxycholic acid, Ca++ = Calcium.

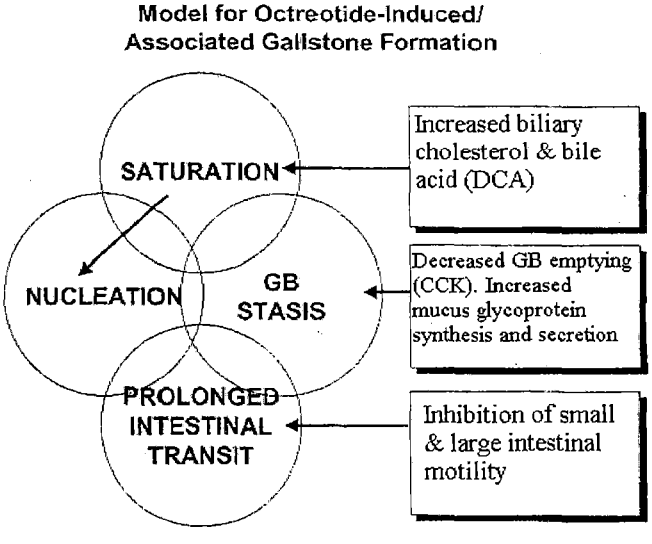

Figure 48. Factors involved in gallstone formation and points at which octreotide may influence gallstone formation; GB = gallbladder, CCK = cholecystokinin, DCA = deoxycholic acid.

VII.V - GASTRITIS

Plöckinger et al reported that acromegalic patients treated with octreotide for over two years showed signs of atrophic gastritis on gastric biopsy specimens without any clinical manifestation[32]. We subsequently asked the Besser group in the UK to conduct a prospective study in 48 acromegalic patients treated and untreated with octreotide[33]. Thirty percent of the patients were found to have gastritis before octreotide therapy versus 47% of the octreotide treated patients. Fourteen percent of patients treated with octreotide for 6-23 months developed gastritis. The authors concluded that gastritis is not an invariable consequence of octreotide therapy even after prolonged periods of treatment.

VII.VI - ANTIBODY FORMATION

With Orskov and colleagues we first reported the development of specific IgG antibodies to octreotide during 2-3 years of treatment for acromegaly in two patients[34]. The presence of these antibodies reduced the plasma disappearance rate of total extractable octreotide by 60 and 80% respectively. The plasma half-life of octreotide in the two patients with octreotide antibodies was 300 and 450 vs. 110 min in those with no detectable octreotide antibodies. A consequence of this immunization was a marked prolongation of the interval of maximum GH inhibition from a mean of 5 to 8 and 10 hours, respectively, in the two patients described.

Subsequently, Kwekkeboom et al reported a case of antibody formation to octreotide, visualised by radiolabelled octreotide scintigraphy[35]. Before therapy (for carcinoid syndrome), no octreotide antibodies were detectable and the patient was treated with octreotide (1000-1500 μg/day sc) for 20 months. Serum samples taken after 20 months of treatment showed a ten-fold increase in radiolabeled octreotide binding (from 2.3% to 22.5%) over pre-treatment levels. Radiolabeled octreotide was displaced from serum by the addition of excess octreotide, thus indicating the presence of specific binding sites. Radiolabeled iodinated octreotide was still increased after a 1:15 dilution of serum was performed. The authors stated that this was the fourth reported case of octreotide-specific antibody formation. In all four cases high-dose octreotide (1500 μg/day or more) was employed. The clinical response of the patient in this study was equivocal, so the authors made no definite conclusion about the ramifications of octreotide-specific antibody formation on the clinical efficacy of the drug. However, increased background radioactivity after injection of radiolabeled octreotide indicated prolonged circulation due antibody-coupled octreotide. Scintigraphy demonstrated radiolabeled octreotide accumulation at the injection site. The authors subsequently recovered octreotide-specific IgA and IgG antibodies from a subcutaneous induration at the drug's injection site.

VII.VII - ENDOCRINOLOGICAL ADVERSE EVENTS

VII.VII.I - Glucose Tolerance

Adverse endocrinological effects are rare during octreotide therapy. Because of its inhibitory action on insulin release, octreotide may impair post-prandial glucose tolerance. Rarely, a state of persistent hyperglycaemia may be induced with chronic octreotide administration. On the other hand, studies with acromegalic patients have shown that octreotide can improve whole body insulin sensitivity by increasing the ability of insulin to suppress hepatic glucose production without affecting its impairment of peripheral insulin action [36,37]. Together with Koop and Ezzat, we studied the effect of octreotide on glucose tolerance in 90 patients with acromegaly[38]. In particular we examined daily blood glucose profiles, oral glucose tolerance and insulinogenic index. We found that while 61% of patients had normal glucose tolerance before octreotide, 20% developed impaired glucose tolerance and 29% developed diabetes after beginning octreotide. In contrast, three of 11 patients who were diabetic at baseline became normoglycaemic or had only impaired glucose tolerance on octreotide. Patients with elevated insulin levels at baseline and females were more likely to develop diabetes mellitus on octreotide. Our conclusion was that glucose monitoring be mandatory during octreotide therapy for acromegaly (*Table 15, Figures 49, 50*).

Number of Patients	Baseline	Octreotide Treatment Glycaemic Status	Number of Patients	%
OGTT (N=90)				
55	Normal	Normal	28	51
		IGT	11	20
		DM	16	29
24	IGT	Normal	10	42
		IGT	10	42
		DM	4	17
11	DM	Normal	2	18
		IGT	1	9
		DM	8	73
Mixed meals (N = 39)				
31	Normal	Normal	25	81
		IGT	2	6
		DM	4	13
3	IGT	Normal	1	33
		IGT	1	33
		DM	1	33
5	DM	Normal	1	20
		IGT	0	0
		DM	4	80

Table 15. Change in glucose tolerance status during octreotide therapy. Overall, patients that were normal pre-octreotide therapy had a greater likelihood of developing impaired glucose tolerance or diabetes than patients who were diabetic pre-treatment becoming normoglycaemic during octreotide therapy.
Percentages represent the proportion of acromegalic patients whose WHO classification for diabetes mellitus (DM) was altered during octreotide treatment as assessed by the oral glucose tolerance test (OGTT) or mixed meals.
IGT: impaired glucose tolerance. (Adapted from Koop BL, Harris AG, Ezzat S. [38]).

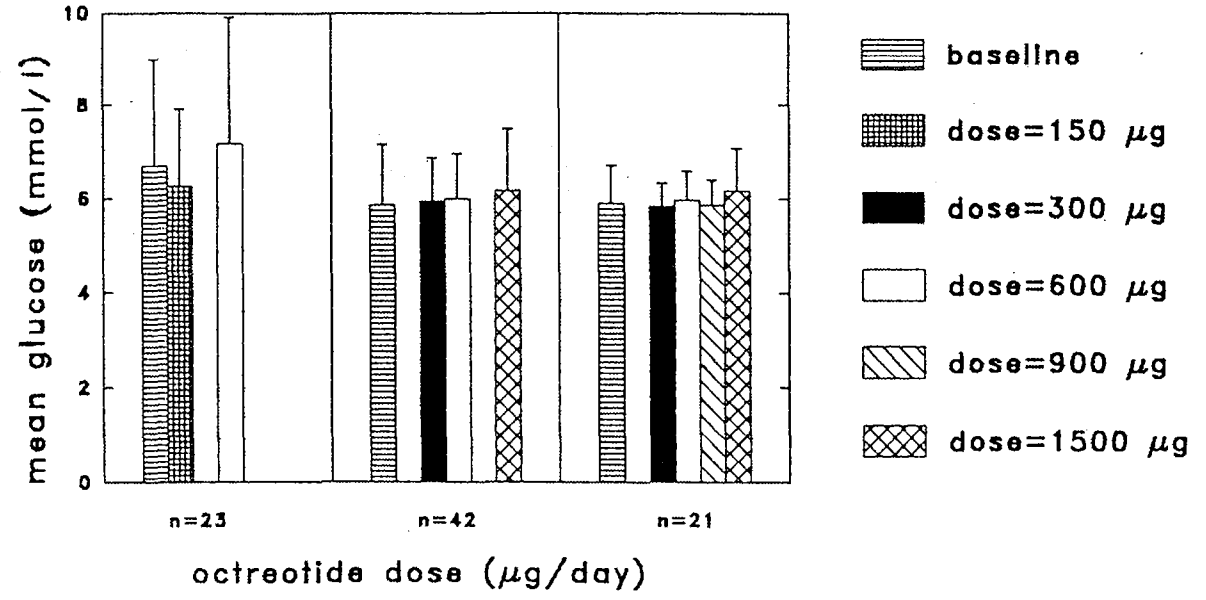

Figure 49. Effect of different doses of octreotide on mean circadian blood glucose concentrations in acromegaly. Values represent the mean of 12-hourly glucose determinations during treatment with the indicated doses of octreotide. (Adapted from Koop BL, Harris AG, Ezzat S.[38]).

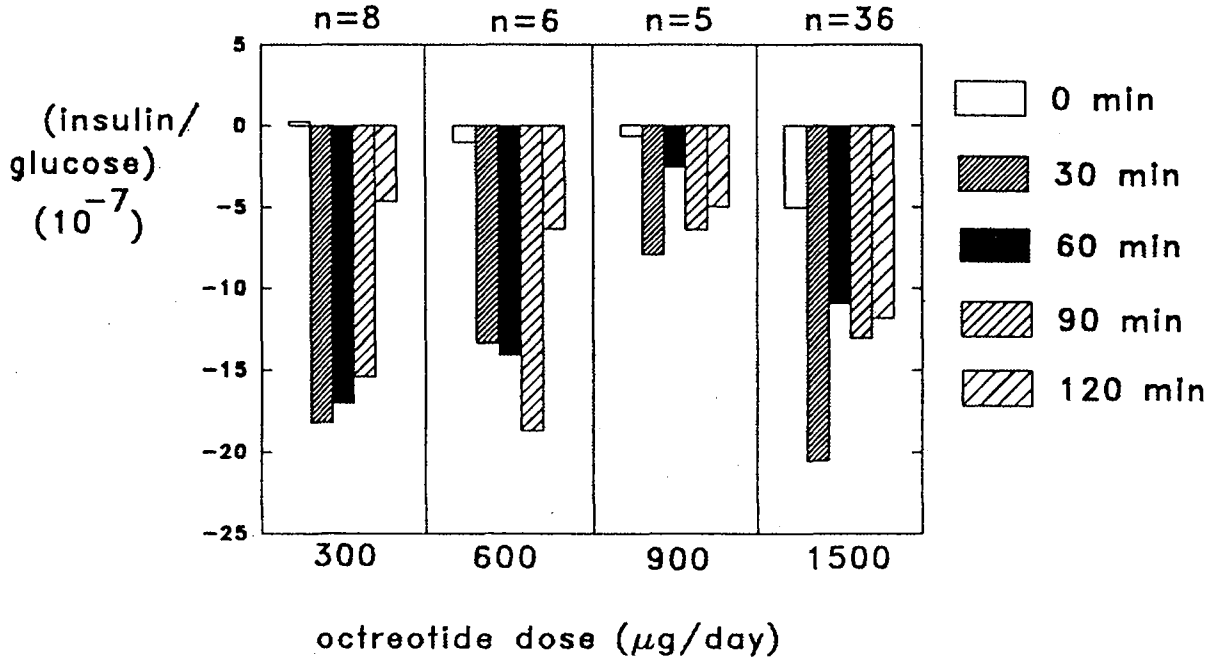

Figure 50. Effect of different doses of octreotide on the insulin/glucose ratio. Values represent median changes of insulin area under the curve (AUC)/glucose AUC compared to baseline in response to oral glucose ingestion during treatment with different doses of octreotide. (Adapted from Koop BL, Harris AG, Ezzat S.[38]).

VII.VII.II - Thyroid Function

With Christensen et al under the direction of H. Orskov we found the effects of octreotide on thyroid function to be minimal. Following three days of continuous subcutaneous infusion of octreotide (100 µg/24 hours), a slight but significant decrease in serum total tri-iodothyronine and a concomitant increase in serum TSH was demonstrated[39]. After an additional three days of treatment, serum, tT3 and TSH had returned to pre-treatment values. The only long-term effect of octreotide was a clinically insignificant increase in serum TSH, possibly caused by a slight inhibition of peripheral deiodination of thyroxine. In a study of seven type I diabetic patients receiving a continuous sc. infusion of octreotide we conducted with Kirkegaard et al.[40] mild transient hypothyroidism occurred but was not considered clinically relevant by the investigators. Rolfsema et al.[41] found that pulsatile secretion of TSH in eight acromegalic patients treated with 300 µg/day octreotide for 1 month remained unaffected.

VII.VIII - CONCLUSION

As outlined above, we made extensive efforts to identify and describe the mechanisms behind adverse events associated with octreotide. Gallstone formation is a recognized complication of octreotide therapy, but our work along with others has helped to define it and we have noted that withdrawal of octreotide leads to rapid return of gallbladder function. Defining the incidence of gallstones associated with octreotide therapy was also a goal during the Clinical Development Program. In 1995, Redfern and Fortuner reviewed the data on octreotide-associated biliary dysfunction and concluded that gallstones occurred in approximately 25% of patients; in most cases gallstones were asymptomatic[42]. Interestingly these data are in line with the more recent findings concerning octreotide LAR, with approximately 25% of patients developing largely asymptomatic cholelithiasis[43]. Verification of our extensive safety program in terms of biliary and other adverse events can be seen from the safety labelling for octreotide, while the descriptions of octreotide in pharmacological reference textbooks note that few precautions are required for patients starting on octreotide therapy.

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Chapter VIII.

Discussion

VIII.I - INTRODUCTION

This chapter draws together the results and lessons of the Clinical Development Program for octreotide during my involvement with the program. Chapter II described the background to the discovery of somatostatin and the inception of pharmacological analogue programs in the pharmaceutical industry. Chapter II also outlined the differences between octreotide and somatostatin that make octreotide a useful therapeutic agent. In Chapter III the rationale behind pursuing diabetes mellitus as a primary clinical indication for octreotide was outlined. Diabetes mellitus proved to be an important learning ground, as the results of our trials demonstrated a good safety profile, which provided us with the background against which we could study octreotide extensively in other disorders. The initial view that the Clinical Development Program in diabetes mellitus was unsuccessful has been reassessed, as octreotide may still have an important role to play in diabetic retinopathy, while the challenge of widespread metabolic syndrome and type II diabetes mellitus means that a polypharmaceutical approach to the treatment of these conditions will need to be considered in the future. Chapters IV and V described the successful program in acromegaly and GEP tumours, where academia-industry collaborations provided cohesive pharmacological and epidemiological data. These data were used in a unique fashion to register octreotide in these indications, and follow-up studies have verified our multi-centre case collections. Chapter IV also outlined other important uses of octreotide, namely, variceal bleeding, fistulae and secretory diarrhoea. Although clinical development studies were pursued for the latter two indications, these were partially unsuccessful due to heterogeneous populations. Variceal bleeding has become a common clinical application for octreotide, and it is employed currently as an effective emergency treatment. In Chapter VI, some of the multiple smaller indications for octreotide were discussed, and their relative successes were highlighted. The manner in which safety research was pursued was described extensively in Chapter VII. This issue was always investigated proactively during my involvement in the Clinical Development Program, and we interacted extensively with academic groups to satisfy the medical and regulatory communities regarding the reliable safety profile of octreotide, particularly in terms of gallstone formation. In the current Chapter some of the key issues arising from my experiences with the Clinical Development Program for octreotide will be discussed as they relate to pharmaceutical research and development today.

VIII.II - MULTIFACETED CLINICAL RESEARCH: THE IMPORTANCE OF AN INFORMED SCIENTIFIC RATIONALE

Retrospective assessment of a large and multifaceted clinical development program, such as that of octreotide, allows one to draw conclusions that are instructive for other researchers in this and other fields. Modern scientific methods and concepts have moved on significantly since the clinical development of octreotide, but it is my belief that the nature of octreotide and the manner in which we studied it are highly relevant for new pharmaceutical therapies today. Modulation of small peptide function has yielded significant successes in the case of cytokines in inflammatory diseases, and many other cytokine and chemokine targeted therapies are in clinical development. These cellular messengers differ from classical hormones due to their pleiotropic nature, as they are involved in the regulation of multiple functions at sites such as the brain, the immune system, peripheral nerves and epithelial surfaces. In this sense, the multiple biological effects of somatostatin are somewhat cytokine-like. Our experience with octreotide in terms of efficacy and safety evaluations can teach important lessons to modern researchers. Primary amongst these issues is the importance of a strong scientific rationale that informs and underpins critical and costly development steps. With octreotide we were able to utilise the body of classical endocrinological research relating to native somatostatin. This revealed to us the wide range of potential indications for octreotide and our plan-

ning was always multi-faceted in nature. Therefore, when the main investigative indication, diabetes mellitus, proved not immediately viable, we had already begun detailed research into acromegaly, GEP tumours and gut hypersecretion/motility disorders. By being based within a large pharmaceutical corporation, it was possible to avail of the organizational and strategic support necessary to develop a strong scientific rationale for octreotide in multiple potential indications. By keeping our focus wide and interacting with key investigators in many specialties, we were able to develop several echelons of active clinical/basic research. Lessons learned in the diabetes mellitus research program regarding carbohydrate metabolism and counter-regulatory hormones were important to demonstrate safety in this regard in non-diabetic subjects. If we had restricted our focus to acromegaly or diabetes mellitus alone, we would potentially have missed the opportunity to identify and study gastrointestinal applications of octreotide like variceal bleeding where the mechanism of action of the drug is largely vascular/non-endocrine. Research today on pleiotropic cytokines in clinical practice could benefit from a multifaceted development program like that employed for octreotide. This necessitates detailed interactions with academic research groups to develop informed scientific rationales, a process which represents a significant organisational and financial challenge for individual biotechnology firms to manage. The large pharmaceutical corporation has the ability to organize and fund such a process of information gathering, which was crucial to the success of our multifaceted program. If a new pharmaceutical agent is developed across multiple indications, it increases organisational complexity but insulates against unsuccessful indications. However, the corporation must ensure that the process of high quality academic data gathering and advice is maintained throughout the clinical development phase in order to predict pitfalls early and benefit from the identification of new indications. At Sandoz, a particular effort was made to maintain a culture of highly scientifically informed decision making. This allowed us to direct research proactively and seek out potential safety issues such as gallstone formation, rather than merely responding to independent observations.

Of particular relevance for smaller pharmaceutical developers is the necessity to maximise the potential applications of the agent being developed. Clinically directed teams may wish to concentrate wholly on potential drug therapies as they yield the greatest benefit for the corporate entity and the patient population. By being over-focussed on therapeutics, the opportunity to develop valuable diagnostic agents may be missed. In the case of octreotide, E. Krenning's and S. Lamberts' groups at Erasmus Medical Centre, Rotterdam harnessed the somatostatin receptor binding characteristics of octreotide to produce an indium-^{111}-radiolabelled analogue. This product, called OctreoScan was commercialised with Mallinckrodt, and has proven extremely useful for the imaging of somatostatin receptor positive tumours [1,2]. The experience gained by this group and others with somatostatin receptor imaging has led to the development of a potential somatostatin receptor directed radiotherapeutic (OctreoTher) [3].

VIII.III - When Concepts Fail: Pitfalls and Opportunities

When assessing the overall impact of the clinical development of octreotide, the relative disappointments are arguably as important as the many successes. Unsuccessful indications and methodologies can help to highlight potential pitfalls for other research groups in industry and academia. As outlined in the section above, we pursued the clinical development of octreotide in various indications on the basis of a strong preclinical and clinical rationale. In retrospect, unsuccessful indications were due in some instances to the logistical challenges raised by restrictive inclusion criteria and patient characteristics than incorrect scientific concepts. At Sandoz, study planning benefited from the availability of high quality advice from scientific and medical experts in the academic community. Thus, our decisions on the viability of indications were based on academic consensus in concert with market research and in-house concepts. Our most important unsuccessful indication was the development of octreotide as a treatment for diabetes mellitus. Indeed, this potentially promising indication was the reason that octreotide received such active initial development. The diabetes mellitus Clinical Development Program was characterised by some successes in terms of metabolic control in type I and type II disease. More importantly for subsequent studies in acromegaly and other conditions, the diabetes mellitus program showed that octreotide treatment was not associated with hazardous or precipitous hypoglycaemia. The importance of tight glycaemic control in preventing complications of type I diabetes mellitus was only becoming apparent during octreotide's clinical development. The Diabetes Control and Complications Trial showed subsequently that lower HbA1c levels achieved with intensive insulin therapy lowered the risk of retinopathy and nephropathy [4]. The most obvious method for improving glycaemic control was escalated insulin dosing, rather than the addition of another injectable drug such as octreotide. The decision not to pursue octreotide as a metabolic therapy for type I diabetes mellitus was probably justified, as subsequent diabetes intervention studies led to the optimization of existing insulin dosing and delivery rather than new therapies. In terms of diabetic complications, final conclusions regarding the value of octreotide cannot be drawn yet. Diabetic nephropathy was and remains today an important cause of renal failure, dialysis and transplantation. As was described in detail in Chapter III, octreotide has been shown in numerous studies to improve renal haemodynamics and filtration indices and is an effective treatment in some animal models of renal failure. The advent of ACE inhibitor therapy as a convenient, safe and efficacious method for retarding the progression of renal disease in diabetes mellitus made further development of octreotide in this indication difficult to justify. In type II diabetes, the control of blood pressure by ACE inhibitors or other anti-hypertensives has been shown by the results of the United Kingdom Prospective Diabetes Study (UKPDS) to be almost as important as glycaemic control in the prevention of diabetic complications [5,6]. An argument for using a somatostatin analogue in diabetic nephropathy could be made if effective receptor-selective compounds were developed. If such targeted therapies were

more effective than octreotide in altering renal haemodynamics and filtration then they might find a role as an adjunctive therapy to preserve renal tissue and prolong time before organ failure and dialysis/transplantation, particularly in patients with an insufficient response to ACE inhibitor therapy. In contrast to metabolic control and nephropathy, diabetic retinopathy represents a major unmet need in diabetes therapy. Patients may undergo rapid loss of sight due to proliferative retinopathy despite adequate glycaemic control. As outlined in the chapter on diabetes mellitus, octreotide continues to show significant potential as a therapy for slowing retinopathy and studies are ongoing with octreotide LAR. The only effective treatment for proliferative diabetic retinopathy is destructive panretinal laser photocoagulation, which is not completely effective in all patients. If octreotide were to demonstrate efficacy in terms of slowing disease progression, it could represent the first specific "retinopreservative" therapy for diabetic retinopathy. Also, preclinical research into somatostatin receptor subtypes in retinal endothelium could point the way to newer subtype-specific somatostatin analogues, although putative analogues would have to have the same good glycaemic safety profile that we showed with octreotide.

The clinical development of octreotide in some gastrointestinal indications was problematic. For instance, the preclinical rationale for treating gut fistulae with octreotide was particularly strong. Furthermore, small studies and individual cases had shown octreotide to be remarkably effective. However, larger studies were difficult to perform and monitor due to the heterogeneity of fistula aetiology, patient health status and individual clinical practice. Similar problems were encountered in studies of post-ERCP pancreatitis, where it was difficult to find consensus on disease definitions. In AIDS-related diarrhoea, individual reports of octreotide use were hopeful, but larger clinical trials were inconclusive. These partially unsuccessful potential indications emphasise the importance of patient stratification and the definition of endpoints, in addition to highlighting the eternal difficulty of performing clinical trials in surgical populations. Since my involvement with the clinical development of octreotide ended, groups from Germany and Italy, with whom we collaborated, have learned from our early negative experiences with octreotide in gut surgery indications. These groups have designed and performed four large, well-designed clinical studies of octreotide in complications of pancreas surgery. These trials stratified patients according to risk, recruited large numbers of patients (over 1000 in total), and applied pragmatic standardised endpoints to assess octreotide's efficacy[7,8,9,10]. In doing so, these researchers have demonstrated a uniformly beneficial effect of octreotide in reducing post-operative complications of pancreatic surgery. This exemplifies the importance of matching scientific rationale with robust, pragmatic trial design.

Finally, the case of octreotide in variceal bleeding deserves consideration. As noted in Chapter V, animal and human studies of hepatic haemodynamics have shown that somatostatin-14 and octreotide reduce hepatic venous pressure. Clinical studies in patients with bleeding oesophageal varices have compared octreotide with all major therapies: Sengstaken-Blakemore tube, vasopressin, endoscopic banding and injection sclerotherapy. Octreotide has demonstrated excellent efficacy and tolerability in the treatment of variceal bleeding. Meta-analyses have favoured octreotide over other pharmacotherapies and found it equivalent to endoscopic procedures, which are treatments of choice[11,12]. Despite these benefits, the gastroenterological community has been reluctant until recently to adopt octreotide wholeheartedly as a treatment for bleeding oesophageal varices. Some of this resistance may come from the idea that octreotide was being suggested as a replacement for endoscopy. Endoscopic procedures combine the ability to diagnose and treat varices definitively in one treatment. As such, octreotide represents a good holding therapy in situations where endoscopy is unavailable or delays occur. Also, octreotide infusions can be used in the acute period to prevent rebleeding by reducing hepatic venous pressure. The weight of clinical experience and positive studies that have accumulated over time have made variceal bleeding a major gastroenterological application for octreotide. Prophylaxis of variceal bleeding in high-risk cirrhotic patients using octreotide LAR could represent a major advance in this high-mortality medical emergency.

VIII.IV - THE INDUSTRY-ACADEMIA DYNAMIC: OPENNESS, COOPERATION AND HIGH STANDARDS

For the industry-based physician to interact efficiently with academic researchers, the relationship must be informed by a sense of mutual trust and common goals. During my stewardship of the Clinical Development Program for octreotide, we made a conscious effort to maximise the links between Sandoz and our academic collaborators in terms of publication of study results. The publication of peer-reviewed results in the literature represented a major goal for our industry-based team, as we viewed this as an independent validation of our academic collaborations. With octreotide, we fostered discussion and debate regarding actual and potential adverse events. From the advice and suggestions of academia sprang an extensive range of studies into the effect of octreotide on carbohydrate metabolism and gallbladder dynamics. The safety debate was undertaken in the public domain in an atmosphere of cooperation between Sandoz and university collaborators. At Sandoz, a conscious effort was made to tease out the potential impact of octreotide on gallbladder function during clinical development and it was seen as an integral part of the program that had to be dealt with in its own right, rather than as an adjunctive issue. It is my belief that such a cooperative atmosphere allows industry and academic researchers to collaborate in the most efficient way and deliver the maximum amount of useful data regarding the efficacy and particularly safety of a novel pharmacotherapy.

The requirement for peer-reviewed data to support sales/marketing efficacy claims was not as evident during the development of octreotide as it is now. If clinical research is designed and implemented with an intention to publish it in peer-reviewed literature, it requires a useful degree of proactive thinking by the industry-based physician. The

peer review process subjects internally developed study concepts and results to independent objective analysis. Peer-review can identify methodological weaknesses and suggest improvements, while demanding of the writer a cohesive explanation of concepts from first principles. Publication of results facilitates debate and challenges external proponents and opponents to encapsulate their positions clearly. Peer review publication is an efficient way of verifying the quality of informed corporate decision making and transmitting the efficacy and safety benefits of a drug to the medical/scientific audience. With octreotide, I was afforded the opportunity of steering many studies through peer-review into print and had to work closely with academic groups to defend study concepts, contextualise results and suggest new avenues of research. This experience is unique to the pharmaceutical physician and provides parallel benefits to the industrial and academic/medical communities when carried out in a forthright atmosphere of cooperation.

VIII.V - THE PHARMACEUTICAL PHYSICIAN

Physicians who hold a position directing the clinical development of a drug have a number of responsibilities. Interactions with academic and clinical colleagues allow the so-called pharmaceutical physician to seek out and identify new indications based on his/her medical training. The pharmaceutical physician is a physician-scientist who interfaces with basic and clinical scientists, patient groups and the corporate environment to guide new drugs from laboratory findings to patient availability. The business environment of the pharmaceutical company allows the physician to call on marketing analysis to assess the potential of new indications identified. In the case of octreotide, this thesis has outlined the myriad of indications that were pursued simultaneously. This was unusual, but was backed by a good understanding of the mechanism of action of octreotide and its safety considerations; many of these indications were at least partially successful. Similarly, medical training and a healthy relationship with academia allow the well-informed pharmaceutical physician to anticipate potential adverse events. We investigated safety aspects of octreotide in an efficient and open manner by acknowledging the increased risk of asymptomatic gallstones. By fostering biliary research we helped to define the nature of octreotide-related cholelithiasis, but also advanced the understanding of the roles played by intestinal motility and nucleation dynamics in gallstone formation. We encouraged the reporting of efficacy and safety data in the post-marketing phase, and acted on relevant data where appropriate. In this way my role in the Clinical Development Program for octreotide incorporated functions of a modern Phase IV post marketing surveillance department.

We sought at all times to promote a culture of peer-reviewed publication of results in the myriad of indications in which octreotide was undergoing parallel development. This allowed us to assess the relative value of pursuing registration based on good quality preclinical and clinical evidence. Also the publication strategy facilitated a regular flow of clinical data into the public arena where the medical community could assess it critically. Critique of study results by non-interested parties provided us with an extra layer of strategic planning in the development of potential new indications. The data gathering abilities of a large pharmaceutical company allowed me to co-ordinate the collection of epidemiological and descriptive evidence on large patient populations in rare disorders. This was particularly true in the cases of acromegaly and TSH-secreting pituitary adenomas. Despite the formation of case registries in the past few years [13,14], our case collection of patients with acromegaly remains one of the largest pharmacological trials in pituitary disease [15]. Furthermore, our data collection led to the publication of a series of 500 patients with acromegaly, which remains the largest patient collection to date [16]. The description of 52 patients with TSH adenomas is similarly a landmark paper in terms of pharmacotherapy of the condition and also in terms of the large number of patients for such an extremely rare condition [17]. It is really only international organizations that can collect such series and physicians in positions of responsibility in pharmaceutical multinationals should be encouraged actively to use the cohesion of the corporate entity to collect and publish valuable information on less common diseases. The success of our combined efforts with octreotide was recognised by the awarding of the Prix Galien to Sandoz in 1991. This international prize is given annually to an outstanding innovative therapeutic agent, and in the case of octreotide recognised the efforts of Pless, Bauer, Huguenin and Petcher (drug discovery and synthesis), Doepfner, Marbach and Briner, Bruns and Weckbecker (preclinical pharmacology), and our clinical research team including Boerlin, James-Dedier, Elton and Dunne.

Recent years have seen an enormous growth in the impact of evidence-based medicine on clinical decision-making and allocation of healthcare expenditure. In many ways this move away from a reliance on the individual opinions of experts (so-called "eminence-based medicine") towards a data-centric view of disease and treatment is laudable. Evidence-based medicine attempts to standardise treatments, thus providing patients with a uniform standard of care. It has been argued, however, that over-reliance on evidence-based decision-making is as fallible as operating on clinical experience alone [18]. Randomised controlled trials apply restrictive inclusion and exclusion criteria to patient populations, which often means that a study's results can be applied to only a limited group of patients in the clinical setting. Our experience with the Clinical Development Program for octreotide in GEP tumours and acromegaly indicates that -for rare diseases at least- the use of a carefully managed inclusive, open label and retrospective approach to data gathering can be useful in studying the disease and the effectiveness of treatment. The validity of our approach is underpinned by the similarity between our retrospective results and the results of prospective controlled trials mandated by regulatory authorities. In contrast to evidence-based approaches, our retrospective case collection did not have to sacrifice the individuality of patients' disease characteristics and their experience of octreotide's effectiveness in the drive for statistically cohesive efficacy data.

VIII.VI - REGULATORY ISSUES: THE ADVENT OF GOOD CLINICAL PRACTICE (GCP) GUIDELINES

It was not uniform among European academic investigators in the 1980's to operate according to GCP guidelines. Fully informed consent with explanations of all potential side effects, maintenance of copious records and standardisation of investigations and disease models were among the practices that had to be introduced with the advent of GCP. The pharmaceutical company sponsoring a GCP trial has various responsibilities including the writing of standard operating procedures, verifying the investigators credentials, co-signing all protocol documents, providing a comprehensive briefing regarding the investigational drug to investigators and monitoring, collecting and analyzing data on efficacy and safety. Analogous responsibilities exist for the monitor and investigator in maintaining the reliability of applied study methods and patient wellbeing. For Sandoz and other multinational pharmaceutical companies, the advent of GCP in Europe represented an opportunity to standardise trial conduct, data collection, data analysis and record keeping across regulatory boundaries. This had the effect of facilitating the use of trials conducted in one jurisdiction, e.g., Europe, in support of regulatory submissions in another jurisdiction, e.g., the United States of America.

In Europe the introduction of GCP guidelines by the Committee for Proprietary Medicinal Products (CPMP) was gradual. The CPMP initially introduced a conduct paper in 1987, which outlined procedures involved in drug testing, trial conduct, ethics and finance. The company had earlier made the decision to adopt US-style GCP guidelines, as it was felt that international adoption of such protocols was inevitable. Also, for trials to be considered by the FDA, GCP guidelines had to be followed, therefore, trials performed in Europe had to be GCP-compliant if they were ever to be used in support of a US filing. Legal adoption of the 1990 final GCP guidelines came in 1991.

With octreotide, the advent of GCP in Europe did not represent an obstacle to the Clinical Development Program. As mentioned above, Sandoz had already adopted GCP standards of ethics, record keeping and consent. Indeed, a full-time GCP compliance officer was in place at the time we began to develop octreotide in clinical trials. The initial indication we pursued was diabetes mellitus, and it should be noted that of the multiple trials in retinopathy, nephropathy and metabolic control, most were placebo-controlled. The good quality of the structure of the metabolic control trials allowed us to make a critical decision rapidly when it became evident that the benefit afforded by octreotide was not clear-cut. In the US, although initial small studies in diabetic retinopathy were positive, clinical and regulatory experts recommended large-scale, placebo-controlled trials if the indication was to be considered further. At that time, a long-acting formulation of octreotide that permitted more sustained suppression of GH and IGF-I was not available to pursue this indication. It is interesting to note that the use of octreotide as a treatment for diabetic retinopathy has undergone a renaissance in the last few years, and long-term studies are underway.

As was described in the relevant chapters, the approval of acromegaly and GEP tumours was pursued using an international retrospective case collection. Typically the FDA required two identical placebo-controlled studies to be performed before considering approval. In the case of GEP tumours this was bypassed due to the compassionate use data. In Europe and other countries worldwide, the acromegaly case collection results were considered sufficiently robust to license octreotide for treatment of acromegaly. In the US, however, despite the fact that the case collection contained two small placebo-controlled trials, a request was made for a further large randomised placebo-controlled study. This delayed the approval of octreotide in the US by about 3 years, and it is a testament to the good practice followed in the case collections and small controlled studies, that the results of the US multi centre trial were virtually identical to the retrospective data. As noted above, a carefully maintained retrospective data set can provide important information regarding real-world patient characteristics, and deliver valid data on safety and effectiveness without resorting to the type of highly restrictive inclusion criteria required for a prospective controlled trial.

VIII.VII - THE FUTURE: OUTSTANDING ISSUES AND UNANSWERED QUESTIONS

In the previous sections I have discussed various aspects of the success and failure of potential indications for octreotide and identified some useful approaches for researchers today. Some issues regarding octreotide are still topics of debate despite the wealth of research conducted to date. The role of octreotide in diabetes mellitus is still being investigated. In particular, the suppressive effects of octreotide on retinal vascular endothelial growth are now thought to be potentially clinically useful. Trials of octreotide in diabetic retinopathy are ongoing and if positive would represent a verification of our clinical development concepts of mid-1980's. In oncology, octreotide has been useful in certain types of somatostatin-receptor positive tumours, but the dosages used have been relatively small. By delivering high-dose octreotide pamoate (rather than acetate) via a LAR preparation, it may be possible to suppress growth in susceptible tumours. Similarly, high dose octreotide LAR or octreotide pamoate at milligram doses or may be used in the future for other clinical conditions such as cirrhosis-associated variceal bleeding. While octreotide has been used in acromegaly for more than 15 years, there has been no assessment of its effects on major mortality/morbidity outcomes such as cardio-respiratory disease and cancer. The average historical age at diagnosis is about 40 years and patients have over double the overall normal mortality rate, with a mean age at death of 57-64 years. Over the next decade we should be able to compare historical data with long-term octreotide-treated acromegalic patients and discover if any decrease in the rate death due to cardiac disease and cancer occurs with octreotide. Eventually, it will be possible to identify the effect of tight or

lax GH/IGF-1 control on morbidity/mortality in acromegaly. If lower GH/IGF-1 concentration has a statistically important effect on major outcomes, then we may see more widespread use of intensive octreotide regimes. Octreotide treatment in acromegaly and GEP tumours has proven effective in the majority of patients. Despite this, a significant proportion of patients have a clinically insufficient response to octreotide, which may be explained by inter-individual pharmacological variations and differing somatostatin receptor subtype expression. Octreotide can be eliminated from the body by routes, such as p-glycoprotein, the expression of which is genetically polymorphic in terms of responses to various exogenous regulators. Combination of octreotide with modulators of p-glycoprotein could increase plasma exposure to the analogue. In patients on multiple drugs for other conditions, physicians should try to choose drugs that have a lower chance of increasing the elimination of octreotide. Patients with a poor response to octreotide may express somatostatin receptor subtypes for which octreotide has a lower affinity. This raises the possibility of designing new somatostatin analogues that have enhanced binding to all somatostatin receptors or to specific subtypes. In the future it may be possible to test for patterns of receptor expression using a family of subtype-specific radiolabeled somatostatin analogues. Thereafter, patients could be treated with individual tailored analogues or cocktails of somatostatin analogues with high affinity for expressed receptor subtypes. Alternatively, advances in gene therapy could be harnessed to increase somatostatin receptor expression by target cells. A new and highly novel study by Mearadji with Krenning and others demonstrated that it was possible to transfect somatostatin-receptor negative colon cancer cells with the sst2 gene and cause liver metastases in rats following portal vein injection of these cells. Treatment of animals who had received sst2-transfected tumour cells with octreotide coupled to a radioactive molecule resulted in less liver metastases than control animals with sst2-negative tumours [19].

Octreotide remains the subject of extensive pre-clinical and clinical research interest, despite the length of time that has passed since it was first synthesised. Its efficacy and safety profiles are well known for both approved and investigational indications. Table 16 outlines these approved and potential uses for octreotide, most of which have been outlined in detail in this thesis. It is heartening to note that many of the prospects for octreotide that were discussed in my review of 1990 [20] have come to be considered as realistic current treatment and diagnostic options. For new analogues, such as, SOM 230 [21,22], BIM compounds [23], and others [24] a full series of safety and efficacy studies similar to those carried out with octreotide will be needed to verify a similar safe balance between effective hormone/cellular growth suppression and avoidance of enhanced carbohydrate and gallbladder adverse events as was demonstrated for octreotide. It must be hoped that highly effective subtype specific somatostatin analogues could represent the advent of primary pharmacotherapy for diseases like acromegaly and GEP tumours.

APPROVED INDICATIONS FOR OCTREOTIDE
Acromegaly
GEP Tumor Syndromes
Carcinoid tumors
Pancreatic endocrine tumor syndromes
Somatostatin receptor scintigraphy ([^{111}-In-DTPA-D-phe] octreotide)
POSSIBLE EFFICACY * OF OCTREOTIDE
Endocrinology (Proven efficacy)
GH pituitary adenomas
TSH secreting pituitary adenomas
Non functioning pituitary adenomas
Gastroenterology/Digestive surgery
Diarrhoeal States
AIDS Related Diarrhoea
Chronic Secretory Diarrhoea
Irritable Bowel Syndrome
Short Bowel Syndrome
Ileostomy
Chemotherapy
Radiotherapy
Grafts vs. Host Disease
Scleroderma
Variceal Bleeding (proven efficacy)
Enterocutaneous and Pancreatic Fistulae
Perioperative Use in Digestive Surgery
Pancreatic Surgery (proven efficacy in reducing complications)
Dumping Syndrome (proven efficacy)
Pancreatic Pseudocysts
Short Bowel Syndrome
Small Bowel Obstruction
Postoperative Ileus
Neurology
Autonomic Neuropathy
Orthostatic Hypotension
Post Prandial Hypotension
Pain Control
* Except where otherwise indicated

Table 16. Approved and potential indications for octreotide.

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Chapter IX.

Directions for Octreotide and Future Somatostatin Analogues in Clinical Practice

IX.I - INTRODUCTION

Approximately fifteen years have passed since the Clinical Development Program for octreotide was begun and in that time biological research has undergone a fundamental revolution. Genetic and molecular techniques such as the polymerase chain reaction (PCR), which are workhorses of the modern biomedical laboratory, were not present even in conceptual form in the early to mid-1980's. A major determinant of the future of octreotide and other somatostatin analogues in clinical practice is the impact that new molecular techniques have made on the way pharmaceutical/medical research is now performed. Data yielded from the application of new technologies to pathological models has provided a new understanding of the mechanisms of disease. In parallel, however, we are now gaining a true appreciation of the immense complexity and inter-connectedness of physiological pathways. Biological research has been cross-fertilised by information technology, as the vast scope of potential patterns of DNA, RNA and protein regulation requires enormous computational power. The current challenge facing the pharmaceutical physician is to avail of the power of genetic and protein expression analysis, while not becoming enmeshed in the huge volume of data produced. Similar advances have taken place in the field of drug design, with the advent of more precise methods of computerised combinatorial chemistry and three dimensional imaging using electron microscopy providing researchers with powerful tools to build and visualise new molecules. These methodologies permit the modelling of receptors, the design of potential ligands, and the analysis of interactions between the two. In the future, this should allow pharmaceutical and biotechnology companies to design better receptor agonists and antagonists (both peptide and non-peptide).

IX.II - ADVANCES IN TECHNIQUES

IX.II.I - Genomics and Proteomics

The robotic automation of the study of genetic and protein expression has led to the advent of the sciences of genomics and proteomics. Thousands of unique genetic sequences can be constructed or printed onto glass slides or proprietary 'chips'. These fluorescently labelled sequences combine with complimentary DNA or RNA contained in physiological samples such as plasma or cell lysates. Comparison of fluorescence intensity for each genetic marker between physiological samples and references allows the identification of upregulated or downregulated genes. Robotic printers are now available for the construction of individual chips/slides at a relatively low cost compared with a few years ago. Therefore, researchers can analyse the expression - or non-expression- of specific families of receptors and growth factors in pathological states. In terms of somatostatin research, gene expression techniques have proven useful in cancer research, where response to octreotide has been difficult to predict. In patients with neuroblastoma, for instance, expression of the sst2 gene, which codes for the somatostatin subtype receptor 2 (SSTR2), was more useful than other patient and tumour characteristics, for predicting disease response and event-free outcomes [1]. Furthermore, sst2 expression in other cancers such as pancreatic cancer can predict response or non-response to octreotide.

Detection of messenger RNA (mRNA) using PCR amplification or microarray technology is useful, but does not predict accurately the final amount of protein expressed. This is because mRNA can undergo degradation or post-translational inactivation, thus decreasing protein concentration. Also simply detecting the expression of mRNA does not take into account downstream inhibitory and stimulatory signals that may come from existing or subsequently expressed intracellular proteins. Proteomics, and other sub-genres, study transcribed proteins, and thus allow assessment of

post-translational modifications of mRNA, and intracellular shuttling/translocation of protein products. Application of this developing field will help to model physiological responses to GH, IGF-1 and identify how octreotide acts at a molecular level. Also, these technologies could help to explain the poor responses of some somatostatin receptor positive cancer cells to octreotide, by comparing relative protein expression with cells that are octreotide-responsive. Furthermore, technologies are being developed which will permit the detection of post-translational changes in proteins, such as the phosphorylation state of a receptor. It is known that phosphorylation of somatostatin receptors occurs and is involved in the desensitization and downregulation of a receptor. Such phenomena can turn off signalling via that receptor. This could be used to determine whether the loss of clinical effectiveness of long-term octreotide treatment is due to receptor desensitization or could be employed to determine whether somatostatin analogue treatment would be effective in the first place, if the receptor (e.g., SSTR2) is fully phosphorylated.

IX.II.II - Antisense Technology

This technology harnesses the physicochemical properties of ribonucleic acids to hybridise small nucleotide chains (oligonucleotides) to them and modulate mRNA/protein expression. By knowing the nucleotide structure of a specific mRNA, an oligonucleotide can be designed that is both opposite (antisense) and complimentary. Intracellular enzymes exist that target abnormal double-stranded mRNA and destroy them. Administration of antisense oligonucleotides can be used pharmacologically to target specific mRNA for destruction, thereby reducing protein formation. This is both a research method and a potential therapeutic tool. In terms of somatostatin analogue research, antisense technology has been used to better define the pathways that cause cell surface receptor expression. In pituitary tumour cells (GH3), it has been reported that sst1 gene expression can be controlled by the growth promoter Pit1 [2]. Administration of Pit1 antisense oligonucleotides blocked Pit1 expression and reduced sst1 and SSTR1 receptor expression. Application of this to other receptor subtypes will help to define the role of genetic promoters and inhibitors in the pathogenesis of endocrine tumours. Such technology can be useful in lieu of the development of selective antagonists for each somatostatin receptor subtype.

IX.II.III - Combinatorial Chemistry

Combinatorial chemistry is now a standard strategy for the identification of selective receptor ligands, whether they are agonists or antagonists. One of the most recent uses of combinatorial chemistry for somatostatin receptor drug discovery was reported by Rohrer et al. [3]. They used combinatorial chemistry together with high throughput screening technologies to identify non-peptide agonists at each of the somatostatin receptor subtypes. These technologies have now advanced to the point that ligands of selective design can be generated against each receptor. This can allow for development of agonists, partial agonists, inverse agonists, or antagonists, which can improve solubility and oral availability, or be designed to be directed to some tissues and not others such as ligands that avoid the central nervous system, for example. This can aid in the removal of drug side effects.

IX.III - ADVANCES IN SOMATOSTATIN PHYSIOLOGY

The five human somatostatin receptors have been well characterised in the years since the clinical development of octreotide [4,5,6]. Radiolabeled octreotide has been used extensively as a research and diagnostic tool to identify somatostatin receptor density in various normal and diseased tissues, primarily endocrine tumours [7,8]. More recently the construction of emitting radionuclide-labelled octreotide derivatives have raised the possibility of specific somatostatin receptor-directed cancer radiotherapy [9]. It is now clear that, although somatostatin receptors all appear to work primarily through G-proteins, activation and recruitment of other downstream adapter proteins occurs. Differential patterns of intracellular stimulatory and inhibitory signals may be apportioned to the activity of various somatostatin receptor subtypes. In different tissues, specific somatostatin receptors may work in different ways. Also, binding of ligands, such as, octreotide to somatostatin receptors may have indirect effects on cell cycle function and protein secretion via modulation of other G-protein coupled receptors or downstream effects on calcium ions and phosphorylation events. A further important potential mechanism of action for somatostatin receptors is via heterodimerisation. It has become increasingly clear that G-protein coupled receptors may heterodimerise with excitatory or inhibitory subunits of other G-protein-coupled receptor components. Through this mechanism ligands binding to one receptor subtype can influence the intracellular apparatus downstream of a second receptor subtype for which it is not a natural ligand. Furthermore, new receptor subtypes can be formed through heterodimerisation, thus increasing the complexity of possible receptor-ligand interactions many-fold. Specifically for somatostatin, heterodimerization has been reported between somatostatin receptors and dopamine receptors, which is of particular significance for pituitary cells which often co-secrete growth hormone and prolactin [10]. The existence of heterodimerisation between somatostatin and dopamine receptor components raises the intriguing possibility of designing ligands specifically to target these heterodimeric receptors and thus inhibit hormonal secretion more readily [11].

A deeper understanding of the relative functions of different somatostatin receptors in different tissues may help to predict response to octreotide therapy:

- Pituitary cell somatostatin receptor expression/function
- Vascular somatostatin receptors in diabetic retinopathy and tumours
- IGF-1/somatostatin receptors and shared downstream targets

- Pro-apoptotic signals mediated via somatostatin receptors; octreotide activates apoptosis in human peripheral blood lymphocytes in vitro [12].
- Anti-inflammatory and immune system activities of somatostatin and its receptors [13]. Does octreotide mediate some of its clinical effects in acromegaly (analgesia, joint cartilage disease, depression) by modulating inflammatory cytokines or glucocorticoid activity via molecular receptor interactions as reported by Chrousos, Tolis and colleagues [14,15]?

Studies over the years have indicated that somatostatin receptor subtypes may subserve distinct physiological functions either because the receptors are uniquely expressed only in some tissues or because they only couple with distinct cellular effector systems and not others. For example, SSTR5 is believed to be expressed in insulin secreting beta cells while SSTR2 is primarily expressed in glucagon secreting alpha cells in animal studies. Since octreotide binds to both receptors, it would be expected to inhibit release of both hormones. However, highly selective SSTR2 and SSTR5 agonists would be predicted to selectively inhibit insulin and glucagon secretion, which has been found in animal studies. Similarly, SSTR2 is believed to mediate effects of somatostatin ligands on gall bladder function. Thus, ligands that affect growth hormone secretion but which do not bind to SSTR2, such as SSTR5 agonists, might be expected to not have the same side effects as octreotide. The importance of relative expression levels of somatostatin receptor subtypes for predicting clinical efficacy of somatostatin analogues, including octreotide, has become clearer in recent years. Pituitary tumour cells that are poorly responsive to somatostatin analogues express significantly lower levels of SSTR2 mRNA and higher levels of SSTR5 mRNA than tumours that are somatostatin analogue sensitive [16]. Studies by Reubi et al. [17,18] have shown that SSTR1 is selectively expressed in prostate tumours. The other somatostatin receptors were not detected in this tissue. This suggests that SSTR1 ligands could be used as selective markers for prostate cancer progression and be used as a possible therapeutic agent.
SSTR2 and SSTR5 have been linked to effector systems involved in cell proliferation and tumorogenicity. Thus, ligands at these receptors would be predicted to inhibit tumour progression, whereas little information exists that SSTR1, 3 and 4 ligands would do the same. Similarly, there is substantial evidence that while all somatostatin receptors are able to couple to G-proteins, their interactions and degrees of coupling differ so that some receptors may induce different cellular actions that other somatostatin receptors because their G protein coupling and effector system regulation differs.

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Chapter X.

Conclusions

The previous chapters have described the conceptualisation, design, implementation and analysis of the branches of the large clinical development program for octreotide during and since my tenure. The development of a robust scientific rationale was a crucial requirement that facilitated the successful pursuit of registration studies for octreotide in multiple indications simultaneously. The cohesive strategic and operational abilities of a multinational pharmaceutical corporation like Sandoz allowed standardised collection and analysis of data in rare diseases like acromegaly and GEP tumours. This approach brought about a major advance in the treatment of these diseases and the quality of our approach was verified subsequently in placebo-controlled trials. The pharmaceutical physician can have a major impact within the corporate and research communities by developing a network of open, mutually rewarding relationships with academic opinion leaders. This industry-academia relationship allowed me to collaborate on the identification of clinical indications and the design and implementation of high-quality clinical trials that were published in peer-reviewed literature. We undertook proactive research into adverse events of octreotide including gallstone formation, carbohydrate and thyroid metabolism. Multifaceted clinical development studies were performed in diabetes mellitus, acromegaly, GEP tumours, gut hypersecretory-hypermotility disorders and cancer. Although the primary indication of diabetes mellitus was not initially successful, research with octreotide in diabetic retinopathy continues to this day, with increasingly positive results. Octreotide has been used in acromegaly, GEP tumours and multiple gastrointestinal indications with great efficacy; the extensive safety data and results of clinical development studies have contributed significantly to our understanding of disease processes (for review see Lamberts et al. [1]). The impact of the advent of octreotide on the medical and scientific research communities can be judged by the large number of publications indexed on electronic databases, such as Medline. Approximately 25% of studies published in the field of somatostatin research are devoted to octreotide, indicating the high level of scientific and clinical interest in this analogue. Modern medical library sciences allow the tracking of articles published in terms of their impact on the literature as a whole. This "citation index" is a measure of how often a study is referenced or quoted in other studies as support for the themes discussed [2]. A citation search conducted in late September 2002 that targeted the articles that form the basis of this thesis demonstrates the continuing interest in key publications, particularly in terms of acromegaly and diabetes mellitus. This search is included as Appendix 2 of this thesis, while the essential bibliography that forms the core of this thesis is listed in Appendix 3.

The Clinical Development Plan for octreotide can be seen as a roadmap for the development of not only new targeted somatostatin analogues, but also to advance novel pharmaceuticals, such as, cytokine modulators of inflammation. Carefully constructed international clinical databases can be used successfully to study the characteristics of complex rare diseases (e.g. acromegaly, GEP tumours) and to measure the effectiveness and safety of a new treatment. Finally, this thesis has outlined how important industry-academia relationships are to the successful and safe development of a novel pharmacotherapy like octreotide across multiple pathologically distinct indications.

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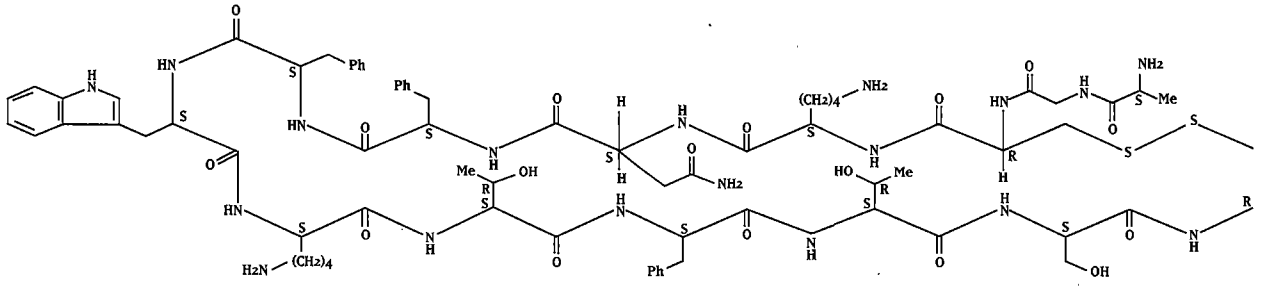
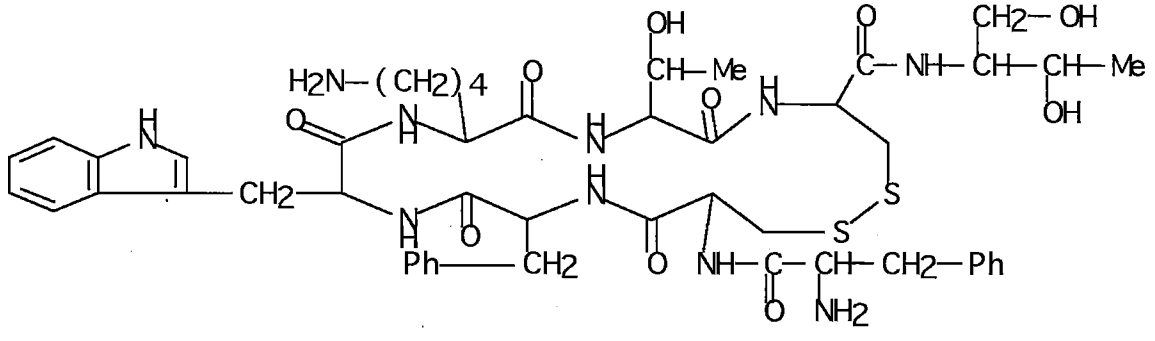
Appendix 1:

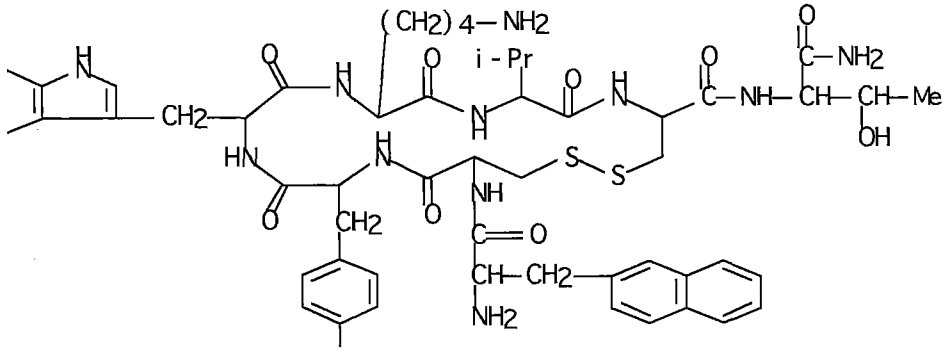
Stereochemical Structures



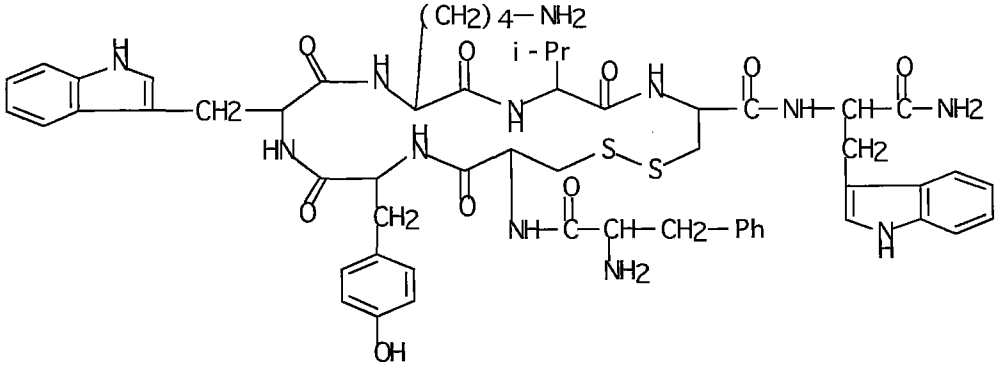
Somatostatin
Absolute stereochemistry.



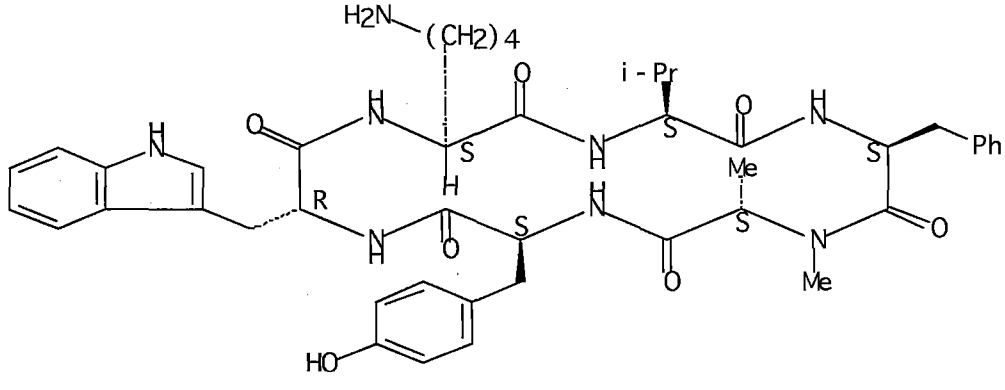
SMS-201-995: Octreotide
Absolute stereochemistry.



BIM-23104: Lanreotide
Absolute stereochemistry.



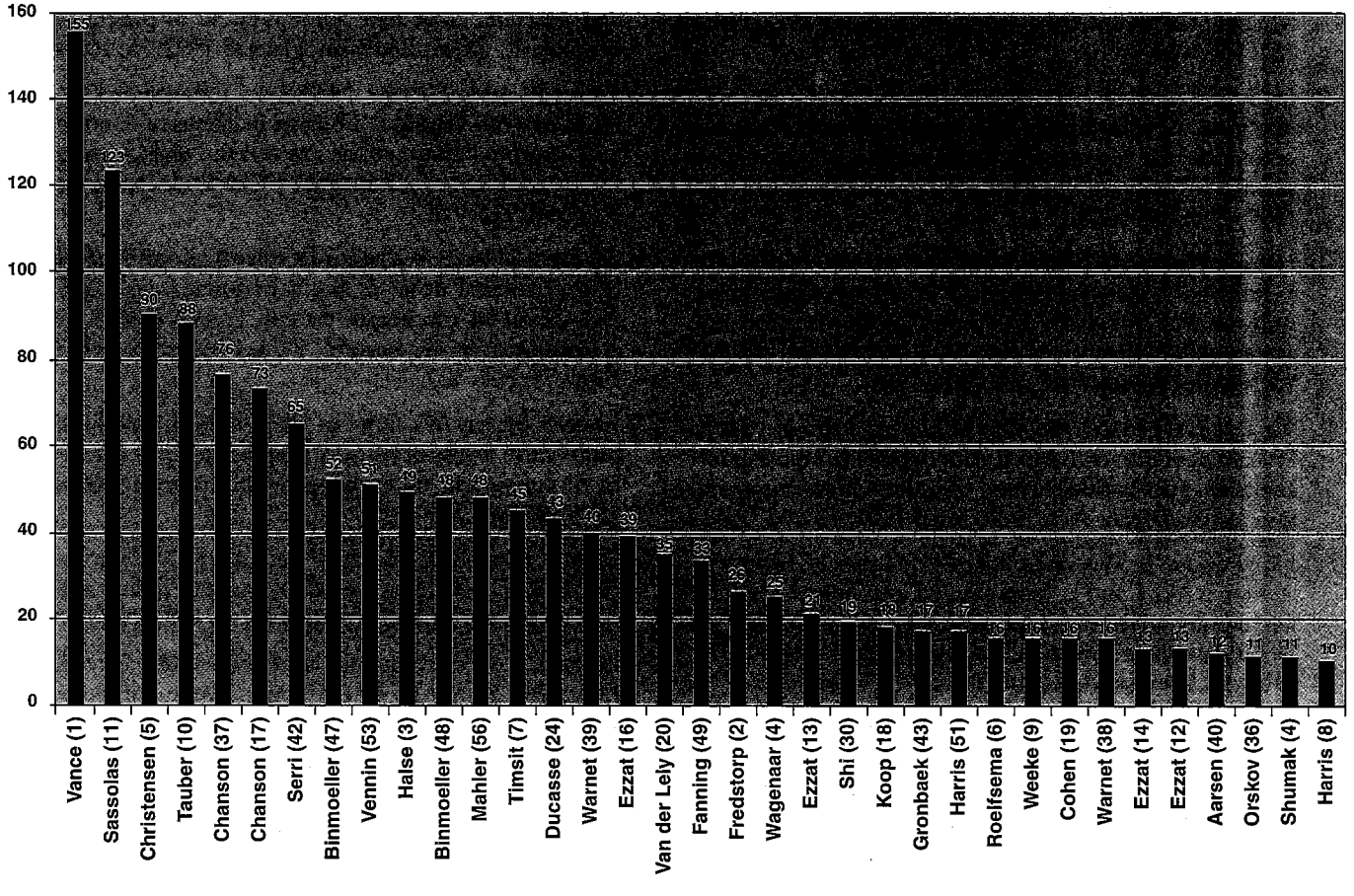
RC-160: Vapreotide
Absolute stereochemistry.



MK 678: Seglitide
Absolute stereochemistry.

Appendix 2:

Citation Index for Core Articles



Numbers in parentheses after author name on horizontal axis refer to listing of publications in Appendix 3.
Numbers on tops of columns refer to numbers of times each article has been cited in other publications.

Appendix 3:

Octreotide Bibliography: A.G. Harris

ACROMEGALY

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Summary

The Clinical Development Program for octreotide illustrates how a dynamic and collaborative industry-academia relationship can maximise the potential of a new therapeutic compound such as octreotide. As a pharmaceutical physician, my involvement with the Clinical Development Program for octreotide from November 1984 to December 1991 (and subsequent close involvement whilst in academia at the University of California, Los Angeles from 1992-1994) allowed us to identify valuable areas of clinical interest and to perform high-quality research in partnership with recognised academic leaders. The main aim of this thesis is to demonstrate how a pharmaceutical corporation can pursue multifaceted clinical drug development when the process is underpinned by an informed scientific rationale that is updated continuously by the best academic advice. This relationship also allowed the pharmaceutical company and I to explore safety issues with octreotide in a spirit of openness and discovery. This openness to new ideas and the availability of cutting-edge academic opinion enabled me to help switch the corporate focus for octreotide rapidly from development of octreotide in diabetes mellitus to acromegaly, GEP tumours and other indications, in which we demonstrated its utility and achieved registration rapidly.

Chapter II describes the discovery of somatostatin and the launching of the somatostatin analogue program. The progress of octreotide through the stages of drug design and the phases of preclinical and clinical development (I - IV) are traced, including the essential requirements for octreotide in terms of its pattern of hormonal inhibition of GH and insulin.

In **chapter III** the clinical development of octreotide in the initial main indication, diabetes mellitus, is described. The presumed role of GH/IGF-1 in diabetes mellitus at the time of the Clinical Development Program is outlined and contrasted with current concepts, particularly with respect to diabetic retinopathy. The medical/scientific and regulatory hurdles encountered during our work in diabetes mellitus are detailed.

Chapters IV and V discusses the success in developing octreotide for use in acromegaly and gut endocrine tumours. The process by which we leveraged the cohesive data-gathering ability of a multinational pharmaceutical corporation to produce patient registries in acromegaly and GEP tumours are of central importance to this thesis, and as such are described in detail. Our work with academic groups worldwide produced published clinical research that advanced the understanding of not only the effect of octreotide on biochemical parameters in acromegaly, but also helped to define disease responses across a wide variety of organ systems. Our experiences gaining registration for octreotide in acromegaly in Europe and in the United States differed significantly, and this thesis discusses how our unique data gathering approach was verified in subsequent formal placebo controlled randomised studies.

The excellent working relationship between academic research groups and myself as a pharmaceutical physician facilitated the development of octreotide simultaneously in multiple different indications. The basic rationales and the manner in which we balanced the various results of clinical trials in gastroenterological (variceal bleeding, fistulae, pancreatitis, gastrointestinal surgery, and secretory diarrhoeas) and other applications (non-growth hormone secreting pituitary adenomas, analgesia) are described in **chapters V and VI.** The consistent reliance on academic advice in these diverse settings allowed us to direct the development of octreotide for clinical use in a multifaceted manner. The outcomes from and validation of this approach are discussed in these chapters.

Chapter VII consists of a detailed description of how we characterised and studied the potential adverse effects of octreotide. This was done in an open and pro-active manner, combining research collaborations and publications with endocrine and gastroenterological groups in Europe, the United States and Asia. Through this approach, the effects of octreotide on carbohydrate metabolism and biliary dynamics are now well understood.

In **chapter VIII** I discuss the results of the Clinical Development Program for octreotide in terms of: the importance of the informed scientific rationale; overcoming failed clinical concepts; openness, cooperation and high standards underpinning the industry-academia relationship; the role of the pharmaceutical physician and the impact of good clinical practice regulations.

Chapter IX points to the future and examines how tools and technologies available now could assist in the development of future somatostatin analogues with enhanced efficacy/safety benefits over octreotide.

The conclusions of the above chapters of this thesis are presented concisely in **Chapter X.**

Samenvatting

Het klinisch ontwikkelingsprogramma van octreotide illustreert hoe een dynamische samenwerking tussen industrie en universiteit de mogelijkheden van een nieuw geneesmiddel als octreotide heeft versterkt. Ik heb van november 1984 tot december 1991 leiding gegeven aan het klinisch ontwikkelingsprogramma van octreotide en ben ook in de daaropvolgende periode tijdens mijn verblijf in het Cedars Sinai Medical Center, Universiteit van Californië, Los Angeles van 1992-1994 als consultant hierbij nauw betrokken gebleven. Deze positie gaf me de gelegenheid om de meest waardevolle klinische onderwerpen te identificeren en om kwalitatief goed wetenschappelijk onderzoek te verrichten in nauwe samenwerking met erkende universitaire onderzoekers. De belangrijkste doelstelling van dit proefschrift is om aan te tonen dat een farmaceutisch bedrijf tegelijkertijd op velerlei terrein een klinisch geneesmiddel kan ontwikkelen indien dit proces wordt ondersteund door een zich steeds vernieuwende wetenschappelijke basis, welke continue wordt geformuleerd door uitstekend advies door wetenschappers. Door deze goede relatie tussen universiteit en industrie was het ons mogelijk om in een sfeer open samenwerking belangrijke wetenschappelijke aspecten van de veiligheid van octreotide te bestuderen. Deze openheid voor nieuwe ideeën en de beschikking over uitstekend advies uit de universitaire wereld stelden mij in staat om de aanvankelijke focusering van mijn bedrijf op een snelle ontwikkeling van octreotide op het gebied van suikerziekte te veranderen naar acromegalie, hormonale darmtumoren en andere indicaties, waarin een succesvolle plaats voor octreotide kort na het aantonen van effectiviteit snel leidde tot registratie.

In **Hoofdstuk I** worden de doelstellingen van dit proefschrift besproken, alsmede de indeling van de verschillende hoofdstukken.

Hoofdstuk II beschrijft de ontdekking van somatostatine en de start van het programma om somatostatine analogen te ontwikkelen. De voortgang van octreotide door de stadia van geneesmiddelontwikkeling en de preklinische en klinische ontwikkelingsfasen (I-IV) worden geanalyseerd, waarbij de basisvoorwaarden voor octreotide ten aanzien van het werkingsprofiel ten aanzien van groeihormoon- en insuline-remming aan de orde komen.

In hoofdstuk III wordt de klinische ontwikkeling van octreotide in de aanvankelijk als eerste indicatie geformuleerde richting: suikerziekte beschreven. De veronderstelde betekenis van Groeihormoon / Insulin-like-growth Factor I in de pathofysiologie van suikerziekte, zoals deze in de begintijd van het klinisch ontwikkelingsprogramma bestond, wordt bediscussieerd. Daarnaast wordt gewezen op de veranderingen in de ideeën over de betekening hiervan, welke zich voordeden in de tijd met name ten aanzien van het ontstaan van retinopathie. De medische, wetenschappelijke en regulatoire moeilijkheden welke zich voordeden tijdens onze studies naar suikerziekte worden besproken.

In hoofdstuk IV en V wordt het succes van de ontwikkeling van octreotide in de behandeling van acromegalie en endocriene darmtumoren besproken. Het proces waarbij we er in slaagden om een samenvattend dossier op te bouwen, gebaseerd op de beschrijving van individuele case histories, de betekenis van een groot internationaal geneesmiddelenbedrijf hierbij, en de mogelijkheid om hiermee patiëntenregisters voor acromegalie en endocriene darmtumoren te starten, spelen een rol van betekenis in dit proefschrift en worden in detail beschreven. Mijn wereldwijde contacten met universitaire onderzoekers resulteerden in breed gepubliceerde klinische onderzoeken welke het begrip omtrent de werking en effectiviteit van octreotide bij deze ziekten verbeterden, maar ook in hoge mate bijdroegen tot inzicht in de biochemisch te meten activiteit van de ziekte en de reactie van vele orgaansystemen tijdens behandeling. Onze ervaringen wat betreft het verkrijgen van registratie voor het gebruik van octreotide voor acromegalie verschilde aanzienlijk in Europa en de Verenigde Staten. In dit proefschrift wordt beschreven hoe onze aanvankelijke unieke benadering van gegevens verzameling via individuele patiënten, uiteindelijk in formele gerandomiseerde placebo-gecontroleerde studies tot vrijwel identieke resultaten leidde.

De uitstekende werk-relaties tussen de universitaire onderzoeksgroepen en mij, als arts verbonden aan de farmaceutische industrie, vergemakkelijkte de gelijktijdige ontwikkeling van octreotide in meerdere, verschillende richtingen. De wetenschappelijke uitgangspunten en de manier waarop we de uitkomsten van de verschillende klinische onderzoeken op het gebied van de gastroenterologie (oesophagus varices bloedingen, fistels, pancreatitis,

maag-darmchirurgie en secretoire diarrhee) hebben geïnterpreteerd, alsmede een aantal andere gebruiksgebieden (niet-groeihormoon producerende hypofysetumoren, pijnbestrijding) worden beschreven in **hoofdstukken V en VI.** De mogelijkheid om continue een beroep te doen op advies uit universitaire kring in deze zo verschillende wetenschapsgebieden, stelde me in staat om de ontwikkeling van octreotide gelijktijdig te sturen in zoveel sterk verschillende richtingen, welke leidden tot klinisch gebruik. De resultaten en de validering van deze benadering worden in deze beide hoofdstukken besproken.

In **hoofdstuk VII** wordt een gedetailleerde beschrijving gegeven van de wijze waarop we de mogelijke bijwerkingen van octreotide karakteriseerden en bestudeerden. Dit werd op een zeer open en pro-actieve wijze gedaan in de vorm van wetenschappelijke samenwerking en publicaties met endocriene en gastroenterologische onderzoeksgroepen in Europa, de Verenigde Staten en Azië. Door deze benadering, bestaat er nu een goed begrip en inzicht in de effecten van octreotide op de koolhydraatstofwisseling en de dynamiek van de galproductie, waardoor clinici de mogelijke problemen goed kunnen vermijden.

In **hoofdstuk VIII** worden de resultaten van het klinisch ontwikkelingsprogramma van octreotide nader geanalyseerd. Hierbij komen aan de orde: het belang van een goede wetenschappelijke basis; de wijze hoe met een falend klinisch concept om te gaan; openheid, samenwerking, en hoge kwaliteit met nadruk op de relatie tussen industrie en universiteit; de rol van de farmaceutische arts en de rol van de regels ten aanzien van "good clinical practice".

Hoofdstuk IX bespreekt de toekomst en welke methoden en technologische vernieuwing ter beschikking staat om nieuwe somatostatine analoga te ontwikkelen met grotere effectiviteit en grotere veiligheid dan octreotide.

De conclusies van de negen hoofdstukken van dit proefschrift worden in het kort gepresenteerd in **hoofdstuk X.**

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My involvement with the Clinical Development Program for octreotide permitted me to make the acquaintance of a large group of individuals, and many provided me with their valuable insights and helpful guidance. I would like to take this opportunity to acknowledge the help of those who provided guidance for this work, in addition to others who have had an important influence on my personal and professional lives. I hope that this list is complete and I would like to apologise in advance for any inadvertent omissions.
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Abridged Curriculum Vitae:

Alan G. Harris M.D.

The author of this thesis received his medical doctorate from the Faculty of Medicine, Strasbourg, France in 1978. He was a full time internist immediately thereafter in private practice and was an attending physician in the department of Hepatogastroenterology at Nice University Hospital, France.

During his tenure (1984-1991) at Sandoz Pharmaceuticals in Basel, Switzerland (now Novartis), he was involved in the clinical development of the first clinically useful long acting somatostatin analog, octreotide (Sandostatin®), approved worldwide for the treatment of gastrointestinal and pancreatic endocrine tumours and acromegaly. His research activities also focused on the investigation of the diagnostic and therapeutic role of somatostatin, analogs in endocrine and gastrointestinal and liver diseases and surgery, oncology, diabetes mellitus and neurology.

In 1992 he was appointed Associate Professor of Medicine of UCLA School of Medicine and Director of the Division of Clinical Pharmacology in the Department of Medicine and Medical Director of the Department of Technology Development and Transfer and Clinical Trials at Cedars-Sinai Medical Center/UCLA School of Medicine, Los Angeles, U.S.A.

He has been Senior Director of Medical & Scientific Affairs, Phase IV Research Unit at Schering Plough Pharmaceuticals, USA, since 1995 and is currently involved in the development of pharmacotherapies for the treatment of allergies,asthma,dyslipidaemias

He is a Fellow of the American College of Physicians, American College of Clinical Pharmacology, and Royal Society of Medicine. He is a member of the Endocrine Society, the American Gastroenterological Society and the American Society for Clinical Pharmacology and Therapeutics.

He is co-chairman of the R&D Committee of the Biotechnology Industry Organization (BIO) since 1992 and member of the Clinical Cardiovascular Sciences Study Section, Center for Review, National Institutes of Health since 1998.