The Hierarchical Genome and Differentiation Waves

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Vol. 3

The Hierarchical Genome and Differentiation Waves

**Novel Unification of Development,
Genetics and Evolution**

Volume I

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THE HIERARCHICAL GENOME AND DIFFERENTIATION WAVES

Novel Unification of Development, Genetics and Evolution

Volumes I and II

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Dedicated in loving memory of Jack Gordon and Pieter D. Nieuwkoop, to
Natalie, and to all who turn their creativity towards the daily rekindling of
life.

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FOREWORD

To have been written by the late:

Pieter D. Nieuwkoop
Director Emeritus, Hubrecht Laboratory
Netherlands Institute for Developmental Biology
Utrecht, The Netherlands

We had the privilege and pleasure of having Dr. Pieter Nieuwkoop (Figures 1 and 2) stay with us on two occasions. We also corresponded for many years. Our letters and visits were filled with discussion of waves, inductions, and the history of embryology. It was during Pieter's second visit that Dick asked him to write this book's foreword. They had a lengthy discussion about how Pieter felt about the book. After some of what Pieter obviously considered a stern warning, he agreed to write the foreword. Unfortunately, he died suddenly in September of 1996, at the age of 79 (Durstun, 1997; Gerhart, 1997), while *The Hierarchical Genome* was in the final stages of preparation. While he read an earlier draft, the version in your hand is one he did not live to see.

Dick and I discussed at length how best to handle the sudden loss of our friend and mentor. We also struggled with how to find a new author for the foreword on such short notice. There really was no one else but Pieter who could do it. Eventually we decided that I would write an account of the conversation they had about the book in general. In this way Pieter could still introduce the book the way I believe he would have intended to.

If anyone is qualified to write this I suppose it must be me. I have lived with *The Hierarchical Genome* since it was a skimpy hypothesis sprouting out of

the slow waves we found together and Lionel Johnson's encouragement of its implications for evolution. When the rapidly growing manuscript was returned from yet another journal because it was far too long it was my idea that it should be a book. I sat in on many discussions and read much of the correspondence during its growth. I was present for many of its key events, including the point where Lionel Johnson said it had grown far too big to warrant him remaining a coauthor, through publication of a partial version (Gordon, 1992a), and finally through a sometimes laborious process of reviewing the final product for clarity and flow.

Figure 1. Pieter D. Nieuwkoop with Richard Gordon at the Fort Whyte Nature Centre, Winnipeg, in 1992.

Above all, I was present during the discussion in which Pieter warned Dick about what he would say in his foreword. I hesitate to use the words of a man with whom I can't double check that I understood him correctly or that I have remembered what he said in the way he would have said it. I also cannot know how much of what he said in a casual conversation he would have included in a formal piece of writing. Pieter was, above all else, a gentle soul, formal and careful in his writing, tactful, preferring to say

nothing rather than to openly criticise. I suspect some of the things he said privately he would not have put in his written foreword. Certainly he would have said some things differently. For this discrepancy I apologise to his memory and hope he will forgive me.

The discussion began with a lengthy critique of what Dick had written about the history of embryology. It was in the midst of this discussion that Dick suddenly blurted out he wanted Pieter to write the foreword.

I remember Pieter laughing with flattered pleasure and then waving one index finger at Dick, his blue eyes sparkling. "This perhaps, you should not ask me, for I won't be kind about everything. I will be honest."

"Of course," Dick replied, "this is what I want, an honest assessment of the book so the reader will know what he's getting into."

At this Pieter sat back and nodded thoughtfully. "I should begin by saying your study of the history of embryology is quite astute. I would say that chapter alone will make the book worth buying. You have researched it well and given insights and perspectives to the problem. I especially like what you wrote about Holtfreter and Spemann. Very accurate and very much in accord with my own memories of those times and people, though I am far too young to remember some of the earlier events."

"Thank you."

"But I must say you speculate far too much. You are not an evolutionist or a geneticist but you have widely applied your ideas to include these fields. Just what you have written about in the embryology alone is revolutionary, entirely new." At this point he leaned forward and emphasised his words with a shaking of his finger once again. "If you are right of course, and in spite of what Natalie has found on the axolotl you have yet to prove your waves are the source of homoiogenetic induction. I personally would do

much more research first before running off on such wild speculations. Without data to back them, they are almost irresponsible."

"I'm not an embryologist either, nor a historian, yet you like what I've done," Dick replied.

"True," Pieter said. "If you have done the evolution and genetic research as well as you have done the embryological then you have done it well indeed, at least in so far as one can learn a field and then speculate without reservation about virtually everything in it!" Pieter chuckled then. "You do not lack, what is that wonderful Jewish word?"

"Chutzpah."

"Ah yes, chutzpah, you have no lack of chutzpah, that much is certain."

"But what if I'm right?" Dick asked.

"If you are right," Pieter replied, "then you will have succeeded in unifying development, genetics, and evolution. This would be a great accomplishment. But your ideas are so far beyond the available data that you will not live long enough to know if you're right. There are generations of work here, hundreds of Ph.D. projects, with whole careers worth of research, proving you are right, or possibly that you are completely wrong. You also assume you are right, and that may be assuming much. I personally still reserve judgment on how right you are."

Now it was Dick's turn to laugh. "If my ideas are properly tested, then even if I am wrong, that's all I want because much new research will be generated and we'll accumulate a lot of new knowledge. What I want to do is provide a fresh perspective on the old problems."

"It definitely is a fresh perspective," Pieter agreed. "So fresh some people may never speak to you again!"

At this point I piped up from the corner where I was listening to all of this. "What do you like about the book?"

Pieter leaned back again, resting his hands behind his head and took a couple of thoughtful breaths. "You have succeeded in amassing an enormous number of widely divergent ideas, all referenced with astonishing completeness. In fact you reference and quote far too much in some places. It is not always easy to read because of this. Nor am I sure I appreciate the proposition format. It makes one think but it's hardly, well, an academic standard. One gets the impression one is following along with you as you think things through and in some places your thinking is a bit muddy I would have to say."

"Still, this will be a tremendous resource for those who wish a picture of the state of biological science at this time. This book, one could pick up in one hundred and fifty years and understand how the biologist of today sees the world. I can think of no major idea, concept, or theory you haven't touched upon."

Dick beamed with pleasure.

"Also, and I think this most important. You have remembered to include the work that came before the present. Many scientists seem to think the old stuff is at best quaint, and at worst mere junk. Certainly not worth reading or paying attention to anymore. In embryology, for example, I frequently despair at the bright young minds that have forgotten or never learned the classical knowledge. Today's embryologist is obsessed with gels and genes. But what is the point of knowing that a gene is expressed in a tissue without understanding even the most basic anatomy of where and how that tissue arose in the first place? Yet I see this all the time."

"I sometimes think they have forgotten the organism they study. This is where you have excelled. You never loose sight of the organism as a functioning whole, nor have you forgotten the significant older works. All

the old ideas are here, right or wrong, good or bad. This book will direct the young minds who read it back to the literature and knowledge as a whole. Perhaps it is a good thing you put in so many references and quote so many people. They will find much that they otherwise would have overlooked. Yes," he finished thoughtfully, "that is what I like best about the work, its completeness."

Natalie K. Björklund
Winnipeg, 1997

Figure 2. Pieter D. Nieuwkoop with Natalie K. Björklund at Kildonan Park, Winnipeg, in 1992, discussing early axolotl embryogenesis.

PREFACE

"Whenever a new scientific concept comes into prominence, it sends shock waves of surprise to the scholars contributing to that field" (Carlson, 1966).

It is my intention to describe a phenomenon that I seem to be the first to have stumbled across with understanding: a quiet wave that forms our very minds. It will crest as it crashes over and forever intertwines the three fields of development, genetics and evolution. The wave forming the brain is there, and many others, perhaps determining every tissue of which we are made. These waves are easily seen with simple tools in common embryos, by anyone who will take the trouble to look. This book is an interpretation of these waves. You may not agree with my interpretation, and are most welcome, and indeed encouraged, to invent other interpretations. But you will not be able to ignore these waves, which will color your view of biology from here on, as they have mine. With the discovery of differentiation waves, it is no longer true that...

"The determination or chemodifferentiation of any given part, i.e. the decision as to what any cell or group of cells shall develop into, takes place invisibly some time prior to the process itself" (Needham, 1931b).

We can now watch it happening.

This book was inspired by a lecture by Lionel (Jim) Johnson given in my Pollution Biology class in February, 1989. (The manuscript was started on June 9, 1989.) When Lionel opened my eyes to fundamentally unsolved and exciting problems in evolution and ecology, he showed how one could leap from population data on arctic charr to possible explanations of the grand sweep of evolution (Vanriel & Johnson, 1995).

I would like to thank Guenter Albrecht-Buehler, Thomas F.H. Allen, Hilary Alto, Karl J. Aufderheide, Penniman B. Austin, Lev V. Beloussov, Teresa C. Binstock, John Tyler Bonner, G. Wayne Brodland, Chris Chetland, Simon Conway Morris, James Cummins, Marc R. Del Bigio, Graham Dellaire, Daniel C. Dennett, Wim J.A.G. Dictus, Hadass Eviatar, Sergei V. Evsikov, David H.A. Fitch, Srecko Gajovic, Helen Gordon, the late Paul B. Green, Gary W. Grimes, Gerhard Grössing, Efroim Gurman, Max K. Hecht, Lewis I. Held Jr., Michael Keller, Glen R. Klassen, James A. Lake, Keith E. Latham, Michael Levin, John A. McCoshen, Andrew D. McCulloch, Ross McGowan, Leonard E. Munstermann, Vidyanand Nanjundiah, Stuart Nelson, the late Henriette C.M. Nieuwkoop-Beukers, Hugh E.H. Paterson, Andrey Polezhaev, Bruce Ratcliffe, Robert Rosen, Cynthia M. Ross, Sharon Y. Roth, Nancy D. Rumph, Tsvi Sachs, Charles B. Schom, Verner L. Seligy, Stanley K. Sessions, William Silvert, Mark Solomonovich, Roland Somogy, Arlin Stoltzfus, Stephen A. Stricker, Michael Sumner, Patrick P.L. Tam, Edward Theriot, Yuri Trusov, Leigh M. Van Valen, Michael W. Vannier, Carey Vigor-Zierk, S. Randal Voss, Richard J. Wassersug, Donald I. Williamson and Kenneth H. Wolfe for critical comments and suggested improvements of draft sections. Thanks are due to Margo Kautz, Kim Nozick, Lana M. Hunstad and Alan W. Hunstad for library assistance, and to Daniel W. Rickey for assistance with digitizations. The following people have bravely tackled reading of whole draft manuscripts: Russell W. Anderson, Natalie K. Björklund, Diana Gordon, C. Cristofre Martin, Stephen P. McGrew, the late Pieter D. Nieuwkoop, and Przemko Tylzanowski. I would not wish to suggest that any of these people endorse all the ideas put forward here. To some extent, this book has become a dialog with them.

The research behind this book was consistently supported by grants from the Spina Bifida Association of Canada (SBAC), an enlightened group of parents who see in fundamental research a possible understanding of their children's condition, which might help the next generation. Partial support was also offered by Abbott Laboratories/Winnipeg Health Sciences Centre, Children's Hospital of Winnipeg Research Foundation (especially through

its former Director, Victor Chernick), Departments of Botany and Radiology and Harley Cohen and Nick Anthonisen, Deans of Science and Medicine at the University of Manitoba, Easter Seal Research Institute, Employment and Immigration Canada Challenge Program, Manitoba CareerStart, Manitoba Hydro, Manitoba Schools Science Symposium, Natural Sciences and Engineering Research Council of Canada, Spina Bifida Association of Manitoba, Spina Bifida and Hydrocephalus Association of Ontario, and the University of Manitoba Research Grants Committee of Senate. The University of Manitoba, especially my former colleagues in the Department of Botany (1984-1994, during which much of the writing of this book occurred), John Stewart and David Punter, and in Radiology, Martin H. Reed, E. (Ted) A. Lyons, I. David Greenberg, and Blake M. McClarty, provided an atmosphere of academic freedom that made this study possible. This book was written in part in the midst of a strike by professors at the University of Manitoba in defense of academic freedom (Gordon, 1996c). My predoctoral, doctoral, and postdoctoral mentors, Edward Anders, Terrell L. Hill, and Robert Rosen, respectively, taught me the importance of academic freedom by their examples.

Two of my students, Kurt B. Luchka and C. Cristofre Martin, provided much of the momentum for the underpinnings of this work. I would also like to thank the innumerable colleagues who responded to my appeals for their reprints, many of whom heard me out in seminars, conversations, and e-mail exchanges, whose ideas are woven into the fabric presented here. I would especially like to thank the staff of the Medical Library of the University of Manitoba, including Ruth Holmberg and Ju-Dai Chuang in Interlibrary Loan (over 300 items), Beverley Brown, Carol Cooke and Bill Poluha in Reference, and Jovy Beltran, Erlinda Erjavec, David Howe, Thomas Quinlan and Moira Raglan in Circulation, and their then Acting Head, Michael Tennenhouse, for their immense effort, along with Ginette Wright and Hung-Hsueh Shao in the Science Library. Thanks are also due to Oeke Kruythof, Librarian, Hubrecht Laboratory, Netherlands Institute for Developmental Biology, who supplied many of Pieter Nieuwkoop's papers, and to Sook Cheng Lim and Yolande Koh of World Scientific Publishing

for their patience and editorial and production assistance in bringing this to fruition.

I have been dragged kicking and screaming by our axolotl embryos back into a now matured molecular biology which I had abandoned in 1964 as an immature graduate student. That approach did not seem to me then (nor yet, alone) to be capable of divulging 'the secret of life'. Not that it didn't make an impression on me being surrounded by the enthusiasm of Aaron Novick (Novick & Szilard, 1950), Jack Sadler (Sadler, Sasmor & Betz, 1983), Frank W. Stahl (1964), Sid A. Bernhard (1968) and the late George Streisinger (Streisinger et al., 1981) at the Institute of Molecular Biology at the University of Oregon. At that time the genetic code was being delivered by emissaries day by day, codon by codon ("Crick (1966b, 1988a) provides engaging accounts of this exciting period of biochemical sleuthing": Mange & Mange, 1990). I now understand part of what was lacking: the very physics and chemical physics I was then drawn to, with skills honed under Susan Meschel (Handler & Meschel, 1993) and Edward Anders in quantitative chemistry. As an undergraduate in his lab, I considered organic matter in meteorites and their relevance to the origin of life (Anders et al., 1964; Anders & Lewis, 1987). Under the eye of my graduate mentor, Terrell L. Hill (1956b, 1960, 1963, 1964, 1969, 1977, 1985a, 1987, 1989), I investigated equilibrium (Gordon, 1968a) and nonequilibrium (Gordon, 1968b) phase transitions and was given the freedom and encouragement to delve into embryogenesis (Gordon, 1966) while earning a Ph.D. in Chemical Physics. On my recent journey back to molecular biology, my constant guide and companion has been Natalie K. Björklund, friend, collaborator, spouse, believer in 'the wave' when it was a 'mere' prediction, and first discoverer of the ectoderm contraction wave in explants and *in vivo*.

Seven embryologists had major impacts on me. (While I nominally postdoced under Conrad H. Waddington around 1970: Waddington, 1972, he was primarily immersed in futurism at that time.) An exciting lecture on embryonic cell sorting by Aaron A. Moscona while I was an undergraduate

at the University of Chicago initiated me into the fascination of embryology and the possibilities for its explanation (cf. Moscona, 1957, 1974). While I was a graduate student at the University of Oregon, I corresponded with and visited Max Braverman in Pittsburgh, who was working on hydroid colonies (Braverman, 1962, 1963; Braverman & Schrandt, 1966). We concluded at that time that it was indeed possible to generate biologically realistic patterns from 'rules' of cell behavior and interaction (cf. Gordon, 1966; Held Jr., 1992). The next problem was to figure out how embryos actually did it (a distinction that unmade leads to arguments even today: cf. Bird & Hoyle, 1994, vs. Niklas, 1994a). During my postdoc with Robert Rosen (1967, 1970, 1991), he set examples of clear and independent thinking in dissecting morphogenesis (Goel et al., 1970, 1975; Rosen, 1970, 1972a,b). I tried my hand at modelling gradients in hydra with the inspiring civil engineer turned biologist, Lewis Wolpert (Wolpert, Hicklin & Hornbruch, 1971; Wolpert, 1991a), in 1969, getting nowhere. After meeting at the 1969 Woods Hole Embryology course organized by Malcolm S. Steinberg, with whom I also later had the pleasure of collaborating (Gordon et al., 1972, 1975), Antone G. Jacobson and I then had the exhilarating and thought sharpening experience of working out how the newt neural plate changes shape (Jacobson & Gordon, 1976a; Gordon & Jacobson, 1978). More recently, I have had the honor and enjoyed the friendship, company and collaboration of that late master of classical embryology, Pieter D. Nieuwkoop (Nieuwkoop & Faber, 1956, 1975, 1994; Nieuwkoop & Sutasurya, 1979, 1981; Nieuwkoop, Johnen & Albers, 1985; Gerhart, 1987; Appendix V: Gordon, Björklund & Nieuwkoop, 1994; Nieuwkoop, Björklund & Gordon, 1996).

Three superb cell biologists, the eclectic diatom electron microscopist Ryan W. Drum (Drum, Pankratz & Stoermer, 1966; Gordon & Drum, 1970, 1994), the late Robert D. Allen (Allen & Kamiya, 1964; Allen & Allen, 1983; Allen, 1987), and the late James F. Danielli (Danielli, 1955; Stein, 1986), gave me a firm foundation in intracellular phenomena and their visualization, while early efforts at what we now call computed tomography of ribosomes with my friend Robert Bender (Bender, Bellman & Gordon,

1970; Bellman et al., 1971), started in the lab and at the suggestion of Cyrus Levinthal (1968), gave me some practical experience in biological image processing, which I parlayed into a second career in medical imaging. Lewis E. Lipkin introduced me to digital imaging in light microscopy (Lemkin et al., 1976).

While I am not an historian of science, I have a curiosity about intellectual history, which I attribute to my so inclined friend John B. Musgrave. If I am right, this work culminates a search that has been going on for well over a century, for the essence of explanation in embryology, representing a vast, worldwide intellectual effort, which I think must be acknowledged. This is why the text is woven through with quotations. I prefer to let previous and contemporary researchers, reviewers and textbook writers speak in their own words, and to retrace the history of ideas. This will exasperate or delight you, depending on your expectations of a scientific monograph. It also allows you to see if you can devise alternative interpretations to mine of what has been said by others. My interest in history does not make me skilled at it, and I have noticed subtle differences in accounts by scientists who turned late in their careers to writing about history versus professional historians of science. Thus the reader should be warned that I take accounts much at face value, only here and there noting contradictions or situations warranting further historical digging. I have not gone to primary sources (unpublished letters, etc.), the way a proper historian does.

The quotes are often extensive to add information beyond my text, and thus generally should not be skipped. Keep in mind that these quotes are selected to support (or occasionally contradict) my thesis, so they may not fully represent the authors' viewpoints. (To enhance readability, I used a colon for a full stop before a quotation, and '...' to indicate no break. If I chose to change the capitalization of a word from the original, the first letter is underlined. I have corrected obvious misspellings rather than using *sic*.) This practice of massive quotation leads to many secondary references, which I have checked when accessible. Any emphases (italics, etc.) are as in the original, unless otherwise indicated (except that genera and species

names are always italicized). My connecting or explanatory words, and editorial comments, are in square brackets (although occasionally, as in $[Ca^{2+}]$, square brackets designate 'concentration of').

I use the common scientific reference style, which gives credit to each idea one builds on directly in line in the text, cumbersome as it may be. Sometimes annoying long strings of references are given, not so much to support my argument by the weight of authority, but to give the reader a broad entry into the literature. I see this text as a beginning of an explanation of embryogenesis, not the final word. There is much work yet left to do, and with a literature so vast and far flung, I prefer to pass on the benefit of my labor by pulling the literature together (nearly 7000 references). For each reader, different aspects will seem tutorial and elementary. Just skip what seems obvious.

An animated set of flip through figures of the ectoderm contraction wave has been prepared by artist and medical artist K. Jack Butler (1996).

It took six starts to decide on a style for this book. It is hard to cross so many fields and keep one's wits. I finally devised a format consisting of propositions, each followed by its justification and corollaries, by rough analogy with Martin Luther's 95 Theses posted in Wittenberg. As the jargon of the many fields is incomprehensible for the uninitiated, as I once was, I have provided a partial glossary, including repeated abbreviations. The reader should note that many common words have specialized meanings in biology, so confusion may sometimes be cleared up by checking the glossary.

I throw a wide net, one with gaping holes due to the uneven state of our intellectual successes in biology. If I seem to claim too much, it is because I am casting for a very large fish, and hope the net holds:

"Aristotle... reports that the Pythagoreans found that acoustical 'harmonies' only depend on (commensurate) ratios of lengths and on nothing else, and that they generalized from this

experience in acoustics to physics and knowledge in general.... It is true that, against their own background, the Pythagoreans were recklessly imprudent when concluding so much from so little. But Isaac Newton was also 'reckless' when proposing that there is a universal gravitational law which subsumes both terrestrial falls of bodies and celestial orbitings of planets" (Bochner, 1966).

I will be accused of trying, but will not attempt, to solve everything at once in this book: there are those brave souls who have tried to see in morphogenesis (Sinnott, 1963; Edelman, 1989, 1992a) or the cytoskeleton (Penrose, 1994, 1995) a solution to the problem of self-awareness and consciousness (cf. Dennett, 1995). I have but little to offer towards the solution of this higher problem, other than perhaps a fresh look at how the brain is built, which may or may not help understand how it functions.

The ideas here are roughly hewn, for that is the imperfect nature of our science of biology and my own understanding. If fragments survive the test of time, and the scorn and mislaid praise of my peers, I will be satisfied with my efforts. If you are dusting off this quaint document a century hence, as I have admiringly done to those of my predecessors, may I wish you the best. Carry on.

Winnipeg, 1998.

FLIP ANIMATION OF THE ECTODERM CONTRACTION WAVE

The following 13 pages should be flipped through by hand to visualize the propagation of the axolotl ectoderm contraction wave. Thirteen clay models were prepared by artist Jack Butler, and each photographed in a subset of the following 6 views:

posterior
left posterior
dorsal
left dorsal
left lateral
left anterior

Each page shows one model, from a few of the above views, representing one moment in time. The time interval between pages is just under an hour (at 20°C). One can see the propagation of the ectoderm contraction wave from the beginning of gastrulation, coincident with its launching as a small dimple, through to its closing down to a small ring at the anterior end of the embryo, where it subsequently vanishes at the end of gastrulation. When it collides with the dorsal lip of the blastopore, the initially circular wave breaks into an arc. At this moment, a crimp in the surface appears to be formed, which may propagate ahead of the wave (not shown) and form a boundary for its trajectory. This wave leaves the neural plate (neuroepithelium) in its wake.

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14.	199	53.	298	92.	409	131.	514	170.	604	209.	707	248.	788
15.	203	54.	300	93.	412	132.	517	171.	609	210.	707	249.	793
16.	207	55.	301	94.	415	133.	519	172.	610	211.	709	250.	797
17.	211	56.	304	95.	417	134.	520	173.	611	212.	714	251.	803
18.	212	57.	308	96.	419	135.	525	174.	618	213.	717	252.	809
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21.	222	60.	320	99.	424	138.	534	177.	622	216.	719	255.	817
22.	222	61.	324	100.	425	139.	535	178.	625	217.	724	256.	822
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24.	232	63.	331	102.	428	141.	538	180.	628	219.	726	258.	825
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31.	243	70.	359	109.	440	148.	554	187.	637	226.	742	265.	844
32.	244	71.	360	110.	441	149.	555	188.	640	227.	744	266.	844
33.	244	72.	365	111.	444	150.	556	189.	645	228.	744	267.	846
34.	247	73.	366	112.	446	151.	559	190.	646	229.	746	268.	847
35.	250	74.	368	113.	447	152.	561	191.	647	230.	748	269.	852
36.	256	75.	371	114.	453	153.	561	192.	647	231.	752	270.	855
37.	259	76.	373	115.	458	154.	561	193.	648	232.	752	271.	860
38.	260	77.	374	116.	464	155.	567	194.	649	233.	753	272.	863
39.	262	78.	376	117.	467	156.	569	195.	658	234.	755		

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