
Introduction

A human Self, a human Person, is — first and last — a biological thing. A human person is a living system, a supersystem of many different tissue subsystems, which are themselves supersystems of many different cell systems, and the human self system is a subsystem of numerous levels of organization up to and beyond its species. You may imagine a human self or person to be also, or instead, some sort of psychological entity, or a philosophical entity, or a moral entity, or even (a container for) a sacred and immortal something or other.

None of those ways of seeing a human person can have any demonstrable reality before or after, or independent of in any other dimension, the biological, cellular entity. The business of being or becoming human can never be understood at any of those levels or from any other viewpoint without an understanding of the structures and functions of the cellular substrates of Life and of Mind.

Everything about human life is cellular in origin and in execution, in the same ways with all other kinds of life we have ever been able to know about. It has beginnings and middles and ends that are like those of all other kinds of life. That is sacred enough.

I became interested in the genetics of schizophrenia [a disorder, as far as we know, entirely peculiar to the human] when I was at or near its most usual age of onset and a close family member was given that diagnosis. The diagnosis was in error; it went away when they made him stay for a while where no amphetamines were available. But I did not learn about amphetamine psychosis until a good little while later. I did already know that some smart people believed schizophrenia to be genetic, and that my ways of thinking had never been exactly entirely “normal” (as I erroneously supposed that those of most other people were), nor were those of most of my family — so I wanted to know more about this thing. I take some comfort in supposing that I have managed to avoid a lot of trouble

in my life by knowing things. That could perhaps be an illusion, or a delusion, but it has worked for me; it is my story, and I am sticking to it.

The twin-study approach was very popular in human genetics at that time, as it has been widely considered a very powerful approach to learning the genetic bases of traits like schizophrenia. Schizophrenia definitely “runs in families,” but it does not follow any known simple pattern of genetic transmission. And that is exactly the sort of thing for which the genetic twin study has been considered most useful. More than 40 years later, we still do not know exactly how that works (neither for schizophrenia nor for any of the other disorders that are distributed over the human population more or less the same way schizophrenia is).

About 1973, while I was brushing up to lead a discussion-group kind of seminar for the psychology department at Kansas State University, studying a book about Irv Gottesman’s and Jerry Shields’s then-recently-published still-definitive genetic twin study of schizophrenia of all time, my wife looked over my shoulder at the case history I was reading and asked: “Why do they tell you that guy is lefthanded?” I didn’t know. I went to the index and looked up everything the authors had to say about handedness. Most of it was in one paragraph not quite three inches long, but that paragraph spread out before me an enthralling puzzle that I have worked on until it now seems to have very few if any pieces missing. I am now reasonably certain that I know what the picture is and can defend my belief.

Briefly, at the primitive level of my understanding at that time, I found an important relationship between twinning and the asymmetry of brain function development, about the asymmetries of brain function in handedness and in schizophrenia. I set out to move myself closer to understanding all of that and preferably to bring the world along with me if I could cause it to work out that way. The question soon enough became “Where do left and right come from in human development?” and I thought I saw a way to approach the question, using twins in a completely different way from any way they had ever been studied before.

The story at the time was that twins have an excess of lefthandedness, and that the excess is concentrated among the “~~identical~~” monozygotic twins because each monozygotic pair must arise from the “splitting” of a single embryo. Somehow a group of cells that “should” make a single embryo must be separated into two subsets that will go on to build two embryos. This was expected to

disturb the asymmetries of forming their embryos to the extent that the split interrupted the building of asymmetries of structure and function that were already underway.

When Mangold and Spemann tied newt embryos in half, back in the 1920s, if they did it just so, they sometimes caused a single newt embryo to develop into twins, and sometimes one of the twins grew its internal organs left-right reversed from the normal configuration. Many people decided that splitting, like that, was a good way to explain the cellular origins of monozygotic twinning and the twin excess of lefthandedness all at once, and it quickly became the standard understanding.

I am not certain that I have ever understood “nature abhors a vacuum” except in the light of how uneasy most humans become at the prospect of having to admit to a complete absence of understanding, and how avidly they will grasp at any prospect of relieving that discomfort.

“~~Fraternal~~” dizygotic twins, on the other hand, have been understood (according to the common knowledge, as if it were a matter of fact without need of any further consideration) to have arisen from “double ovulation” — the more-or-less simultaneous release of two egg cells from two separate, independent, parallel ovulations, from two unrelated follicles that need not even be in the same ovary or the same ovulatory cycle. The symmetries and asymmetries of their embryonic development are therefore not disturbed, have no reason ever to be disturbed, and therefore dizygotic twins can be expected to be exactly representative of development among the embryos and fetuses of the single-born remainder of the population.

So, my idea was about as straightforward as anything ever is in the study of human development: By studying the differences between monozygotic twins with their odd embryogenesis, and all the normal, everyday singletons like the rest of us, I should be able to learn something about how the “normal” embryogenic processes work by studying how the people who turn out differently get that way. The “rest of us” could be represented perfectly by dizygotic twins, serving as experimental controls for any possible difference that might be due to some aspect/s of simply physically being twins..., such as sharing the space and

resources of a womb. DE - Cells and Embryos, Twins and Chimeras, Left and Right, Mind/Self/Soul, Sex, and

Schizophrenia

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4 *How New Humans Are Made*

As it turned out, as things went forward, my results, time after time, every time, from the very beginning, from every angle from which I could find a way to question it, told me that the old stories were all wrong. I also began to learn how severely limited are the powers of fact and truth on the one side, against false but comfortable common knowledge on the other.

Arguably, the first “big” thing I did was to collect handedness data from a large sample of twins and their families. With the very substantial help of our National Organization of Mothers of Twins Clubs, I gathered 773 usable three-generation twin families, with handedness data on over 10,000 people. [I got over 800 responses from 500 questionnaires I sent to their annual meeting that year — I have never seen or heard of any 160% questionnaire efficiency before or since.] It *is* true that twins are more often lefthanded or ambidextrous than are general population singletons. It is *not* true that it has anything to do with the circumstances of twin pregnancy. It has nothing to do with which twin spends more time “on top” in the uterus, or with anything we understand about how a pregnancy turns out to be twins. It is *not* true that monozygotic twins account for all or even most of the difference. Monozygotic twins do not in fact have any higher frequency of lefthandedness than the dizygotic twins have.

Nothing about twinning itself causes nonrighthandedness, and I know this because the single born siblings of the twins in these families also include more lefthanders than the singleton population, statistically no different from the frequency among the twins.

The parents of the twins have a higher frequency of lefthandedness than their own siblings (the aunts and uncles of the twins) who are not themselves parents of twins.

So ... twins do not get their excess lefthandedness from anything about the biology of becoming twins or anything about just physically *being* twins. They inherit their excess lefthandedness from their parents, and so do their singleborn siblings. Each lefthanded parent (mother or father equally) increases the chance of lefthandedness among their children by a factor of about 1.5 (children of one lefthanded parent and one righthander are about half-again as likely to be lefthanded as the children of two righthanders). Families with both mother and father lefthanded have about 2.25 ($=1.5 \times 1.5$) times as many lefthanded children as two righthanded parents have.

There are also certain malformations that are excessively frequent among twins, again attributed to the monozygotics for the same reason, because the malformations in question are symmetry malformations, “midline” or “fusion” malformations, presumably disturbed by the “splitting.” They are anomalies of structures formed in the process of building the embryo by the fusion, in the midline, of not-exactly symmetrical left and right half-structures. In anencephaly and spina bifida, the neural tube does not close properly, leaving the spine or the skull open and the nervous tissue inside poorly formed, if at all. In the orofacial cleft anomalies, the parts of the face are not fully and properly grown together into nose and lips and such. In the congenital heart defects, the cardiac tubes that will form the heart after fusion in the midline and remodeling either skip part/s of the process or do it wrong.

All of these most common major malformations are also in excess among the parents, siblings, and/or offspring of twins, and there is no difference between the families of monozygotic twins and the families of dizygotic twins. All of these malformations are also associated with an excess of lefthandedness in their non-twin victims, and among the first-degree relatives thereof.

I did a good bit of work with some dental diameters data I was given by Professor Rosario Potter, comparing monozygotic and dizygotic twins, and later singletons — more fascinating results. Examining those data with multivariate statistical procedures, the programs can in fact tell the monozygotic and dizygotic twins apart (the individuals, not the pairs; nothing to do with pairwise relationships), but they are much more alike than either is like the singletons. Both groups are far more different from singletons than they are from each other.

The greatest multidimensional distances are between singletons and twins (of both zygosity, equally again). Classification is about as perfect as biology ever is. Not one person identified as a twin in that sample was ever misclassified as a singleton. A very small number of singletons were classified as twins in some of the results. By the time we get to the end of this story, that fact will make all the sense in the world because most people who grow from twin embryos to live birth are born single. [Explaining how I know that deserves a whole chapter, later.]

Those multivariate discriminant function analyses can distinguish the size measurements of teeth in left sides of the mouth from those on the right sides,

among the singletons, but not among the twins of either “kind.” The twins — both zygosity groups equally — are extraordinarily symmetrical in the sizes and shapes of their teeth — missing the small normal asymmetries of dental development.

Those statistical programs can also tell the sets of tooth size measurements apart by sex with very high accuracy, as long as the subjects are singletons or members of same-sex pairs. Boy-girl twins cannot be sorted by sex with these measurements of craniofacial structures. As it turns out, a number of other variables can be lined up with these. The members of girl-boy twin pairs are not quite exactly like any other people of either sex, twin or single. That, too, deserves and gets a chapter of its own.

The old common knowledge is false.

The observations I have collected are loudly incompatible with the idea that monozygotic and dizygotic twinning are very different processes. Every anomaly that is present in excess among twins has been attributed to the monozygotics because of their “splitting,” and dizygotic twins have been presumed to be innocent of all such variations. That is absolutely wrong. Everything that is odd in any way about the embryogenesis of monozygotic twins is more or less exactly as odd among dizygotic twins, except when it is more so among the dizygotics.

In every situation where there is a difference between monozygotic twins and dizygotic twins as groups that is too large to be due to sampling error, the dizygotics are the ones who have it worse.

Dizygotic twins cannot be arising from any kind of embryogenesis except exactly the same system of processes that result in monozygotic twins.

How can they do that, starting with two independent egg cells?!

They cannot.

So, how do they do it if they don't do it the way “everybody knows” they do it?

This is the story of how a classically-trained, philosophy- and theology- and psychology-literate behavioral and developmental geneticist has gone about

seeking answers to such questions, set in a frame of what it means to become a human in the first place.

If there is a science a person needs,
then it is the science I teach, that is to show a person his place in the world
and what you should be in order to be a person.

Immanuel Kant

There is no more complex question anywhere than the ones about how humanness in general, or any particular individual human, happens. I cannot make it quite simple and still tell you the truth as we best understand it, but I think I can make it much clearer for you than it probably is now.

... the history of man for the nine months preceding his birth
would probably be far more interesting
and contain events of greater moment,
than all the three score and ten years that follow ...

S. T. Coleridge

In almost 200 years since Mr. Coleridge left that thought behind in passing, we have actually made considerable progress on many fronts toward learning much of what it seems he would have liked to see. It may be that the only part he had wrong was the word “probably.” Except perhaps for some variation in personal points of view among those considering the question, I believe we have advanced the question well beyond the probability that he conjectured

A true scientist is bored by knowledge;
it is the assault on ignorance that motivates him.

Matt Ridley

Any sufficiently advanced technology
is indistinguishable from magic.

Arthur C. Clarke

Yes, so be it, and all living systems are sufficiently complex that they are indistinguishable from miracles. However, to call anything magic or miracle

without even trying to understand it is at best no fun, and arguably, from at least any scientific sort of viewpoint, irresponsible.

I have thought for years that it would be wonderful to start some sort of written thing with the sentence, “Each of us was once a single cell,” or to use that as a title for a writing effort about human developmental genetics. Of course, the single cell I had in mind was the zygote — the single cell that is often simply, but not quite correctly, called “the fertilized egg cell.” That is a fascinating thought, very evocative, and I thought for a while that it would make a great title for a book more or less like this one. Further reflection brought me very near, for a different while, to abandoning that idea no matter how lovely it sounds. You see, that lovely-sounding idea is one of those lovable, comfortable, simple ideas that are just a little too simple to be true. It is, however, a great lead line and a wonderful little lie because it is the theme on which the truth is a fascinating variation. I have decided to use it after all and clean up the part that is not true later. The difference, the reason why and the extent to which it is not quite true, is a major component of why this particular story needs to be told. As I hope and expect to make clear in these pages, an astonishing fraction of us never were entirely contained within a single cell, even in “potential” form or substance. There will be more about that when we talk in greater depth about chimeras, and about “potential”.

No question has ever arisen in any human mind that is more complex or compelling than the questions many of us have about who and what we humans are and how we came to be as we are. Those of you who are satisfied with answers to those questions that have been delivered as articles of faith may want to put this down and walk away, now — to just step around the possibility that this will make all of that harder for you to hang on to. If you would be lost without those comforts, it is just as well for all concerned that you stay where you are and do not try to follow along. Much of this material does have strong prospects of increasing your comfort with rational versions of answers like those, but only with the rational versions.

Along one of its several paths, this is all about efforts on the part of human minds to understand human minds as a part of the business of becoming and being human — as individuals and as species. I hope to give you a comfortable understanding that being human has no need of meaning outside of the place

it holds in that grand continuum of being that is occupied by all living things, and that all we need of miracle and wonder and transcendence and ineffability is comfortably contained in thoughts just such as those.

Life on Earth may well have begun in any number of times and places, but every scrap of the huge body of evidence that we have been able to discover so far tells us that only one of those beginnings succeeded and endures today. The life sciences of the last century or so have gathered and made available an overwhelming mass of sound evidence that *all of Life as We Know It* has come from a single source/“event”/process, has not finished unfolding, and will not finish unfolding in any foreseeable part of the future.

Human life is a part of all that, in no demonstrable way above it or beyond it, and cannot in any way be understood as separate from it. Human life cannot be understood except in the perspective of the place human life holds among all living systems.

I have had occasion to see and hear philosophers (real live professional living-and-working-for-a-living-today philosophers) acting as if they are certain that questions such as those belong exclusively to their domain. However, I can assure you that any answer to those questions which is not biological in substance is empty nonsense and a waste of time. Everything you are, everything you do, everything that happens between your scalp and your toenails, between your ears, and between your legs ... is done by cells, and I can prove it.

There is a glossary at the back of the book to give you definitions for words the meanings of which might not be right away comfortably clear to you. There certainly are other definitions elsewhere for some of those words, but the definitions in this book's glossary will be the ones about what the word means in our present context. There is also an index that should help you look ahead to find more quickly any of the ideas in here that I don't get around to writing about close enough to the front of the book to suit you.

At this time in human cultural evolution, when the Internet puts an enormously generous sample of all the information in the world at our fingertips, all of the background material in here is within reach of the kind of Web search that anyone who can read this can do. We have available the general-purpose search engines like Yahoo® and Google®, and “metasearch” engines like Dogpile®

and WebCrawler®. Then there is PubMed, a very usable route to the primary biomedical literatures of the world, provided by the National Library of Medicine at the US National Institutes of Health. All of them have built-in ways to help you learn how to make them work. The most important variable component of your effectiveness and efficiency as a Web-searcher is the business of guessing the best search keywords for getting what you want. As far as I know, that can only be improved with practice. It will evolve, you see, under the selective pressure of your curiosity and ideas. If the first bunch of answers you get contains anything at all useful, find one or more words that the useful returns have in common, and use those for a new search.

Some profoundly fundamental concepts will show up at issue here, where most of what people have believed about fundamental events or components of human prenatal development has been wrong, some of it for well over a century so far. In all such cases, I hope to explain a plausible alternative and to offer ways to understand whatever might have been plausible about the substance and the origins of those old errors. It is often of serious interest to consider how so many otherwise apparently reasonable and intelligent people could have gotten it so thoroughly wrong for so long.

The story of human prenatal development is nothing short of fascinating and full to bursting with wonders. I am convinced, and I hope that I will leave you convinced, that the cellular truths are even much more wonderful than the simpler superstitious imaginings of the past which I hope and expect to replace. When you know something about how, and how many, and how often, things can and do go wrong in the unfolding of what might eventually become a new human individual from the contents of a single cell or two, the wonder grows still more.

If you will think through that last thought again without restricting your thinking to the “human” situation, you will find that the wonder is no less. When you think of the human organism as a bridge to be designed and built — which it is, for the “purpose” of continuing the species by carrying a particular, unique version of the human genome from one generation to the next — then all concerns you might have about the intelligence behind its design should find their focus dramatically shifted. There is much more and greater intelligence in the Universe than any imagined counterpart or version or extension of Mind in the image of Man.

The development of any complex organism is without room for doubt not an event, but a process — a proceeding, a procession, of events most of which cannot be explained in detail within the confines of what we know of natural law. That, by the way, is as good a definition of “miracle” as there is to be found. It is my duty, my passion and my mission as a scientist to demystify mysteries and to run miracles to ground, but I am under no illusion of expecting ever to take definitive care of all of them.