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# Direct physical formation of anatomical structures by cell traction forces

## An interview with Albert Harris

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Albert Harris was educated at The Norfolk Academy, Norfolk, Virginia, USA (1961). He then earned a Bachelor of Arts Degree in Biology from Swarthmore College, in Pennsylvania, USA (1965), followed by a Ph.D. in Biology (1971) from Yale University, where his Dissertation Advisor was the great John Phillip Trinkaus. He held a Damon-Runyon Postdoctoral Fellowship in Cancer Research in 1970-72, under Michael Abercrombie, FRS, at the Strangeways Research Laboratory of Cambridge University, England. Then he accepted a position as Assistant Professor in the Zoology Department of the University of North Carolina at Chapel Hill, N.C. USA. In 1977, he was promoted to Associate Professor of Zoology, and in 1983 was promoted to Full Professor of Biology. In Oct.-Nov. 1991 he was honored to be Distinguished Visiting Professor of Zoology at the University of California at Davis.

**How did you initially study force fields in living tissues and what was the response of the scientific community to your findings?**

We began by using thin protein gels to study the propulsive forces by even centimeters. In some of our experiments, cell traction rearranged and aligned collagen gels and embryonic muscle fragments to form anatomically-realistic patterns. In further experiments, fluorescently-labeled collagen was injected into chicken embryos, where forces rearranged it to form anatomical patterns.Histological sections of the body give no indication of the powerful force fields that exist in the living tissues. Our research proves these forces are able to rearrange cells and collagen to form tendons and skeletal muscles, and suggests this is the normal mechanism by which these and other structures are formed in embryos. We had hoped that opponents of our hypotheses would criticise them openly in print, would propose alternative explanations for our observations, and do experiments to disprove our conclusions. Instead we met a stone wall of silent opposition, few citations, and no funding.

**Over 20 years ago, you and your colleagues published a series of papers on forces exerted by individual cells, first on elastic rubber substrata and later, on collagen gels. You discovered that these forces produce normal-looking anatomical patterns. In my view, these experiments deserve to be ranked among the most instructive in the entire field of developmental biology, even comparable to Driesch's separation of sea urchin blastomeres, Spemann's organizer and so on. What do you regard as the main significance of this research?**

I am flattered by your opinion of our research and grateful for this opportunity to summarize what we discovered. Patricia Wild

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**Professor Albert Harris with his children in 1980,** *about the time when he, David Stopak and Pat Greenwell began to realize the true significance of their observations on silicone rubber substrata and the mechanical reorganization of collagen gels.*

(now Patricia Greenwell), David Stopak and I showed that cells can create geometric patterns directly by means of traction forces (Fig. 1). They don't need to have a chemical pattern first, to which cells then respond.

Fibroblasts turned out to be at least a thousand times stronger than expected. We wondered why such strong forces wouldn't distort normal structure-creating mechanisms inside embryos. Eventually, we realized that these forces are a central part of those mechanisms. We think they align tendons, ligaments and muscles and compress collagen into organ capsules, dermis and dermal papillae. We felt like cave explorers, when they unexpectedly find a large undiscovered room, where no one has been before and from which further rooms open in different directions.

The key point is that the mechanisms by which fibroblasts crawl are used, inside the body, like powerful winches. The strongest cells produce long-range effects as much as 6 centimeters away, in collagen gels. Of course, it works even better at closer ranges, of millimeters or less. Mechanical stress is a very efficient alternative to diffusion gradients. It can act faster, at longer ranges and even transmits more «information». Instead of just having an amount at each location, stress and strain have directionality. In mathematical terms, they are tensors rather than scalar variables.

Like other developmental biologists, we were trying to find the chain of causes by which genes cause anatomy to form. We had assumed that cell movements and force exertion were at the far end of this causal chain, at the opposite end from genes. But the patterns formed in our cultures proved that physical forces can also be middle parts of this causal chain. They can directly create long-range, large-scale geometrical patterns. Chemical signal patterns don't always need to come first, as most people seem to believe. We think more in terms of feedback loops between chemical signals and mechanical forces, with each controlling the other. These feedback loops are geometric equivalents of homeostasis, creating and maintaining anatomical shapes.

**How did you get into biology?**

Originally, I wanted to be an artist and paint pictures for a living, like my father who was famous in his time. Thousands of his paintings and prints hang in museums, offices and homes. But I just wasn't a very good artist. Then I wanted to be a herpetologist; I have studied turtles and snakes all my life and went to college expecting to become some kind of «whole animal» biologist. I also worked two summers at marine laboratories and did a lot of diving with compressed air tanks. Spatial patterns of any kind, artistic or biological, were my main interest. My mother was a medical doctor and I loved to look at protozoa through her microscope and at anatomical diagrams in her medical school textbooks. She also gave me Paul DeKruif's famous books to read and a few times she saved people's lives right in front of me, such as when we were shopping and somebody had a heart attack or a seizure. The power of medicine can be impressive.

**What about the flexible substratum research?**

I did my Ph.D. work with J.P. Trinkaus, whose specialty was in forces inside embryos. The first edition of his book «Cells into Organs; The Forces that Shape the Embryo» was written while I was his student and that subtitle is exactly what we wanted to discover. I had wanted to study cell sorting and then asexual budding in sea squirts. But my dissertation was sort of a natural history of tissue culture cells, their movements, locations of adhesions, responses to adhesive islands and side views of

**Fig. 1. Two groups of fibroblasts reorienting collagen in a gel.**

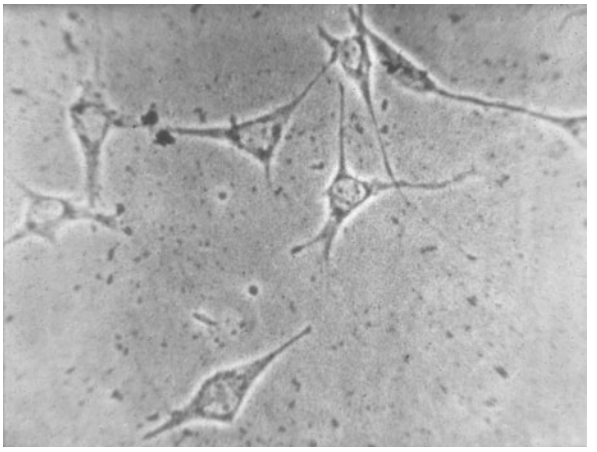

**Fig. 2. Fibroblasts crawling on the surface of a thin fibrin clot**, *with the movement of particles of carbon used to determine the locations and directions of traction forces. This is a frame from a time lapse film, taken in the fall of 1971 and shown at a Ciba Symposium in Sept 1972 and later at many other meetings.*

ruffled membranes.

I will always be grateful to the Damon-Runyon Foundation for granting me a postdoctoral fellowship to work with Michael Abercrombie, who was just then (1970) moving from London to Cambridge. Neither my wife and I had ever been to Europe before, so this was a great adventure for us, although we had driven all over Mexico.

The Strangeways Laboratory in Cambridge had pioneered tissue culture and they still used clotted plasma as a substratum for culturing cells. I noticed that fibroblasts distorted these gels and remarked to Professor Abercrombie that this must be the dehydration phenomenon that I had read about in Paul Weiss' papers. This was only the second or third conversation I had with Professor Abercrombie and he said that probably these distortions were side effects of the propulsive forces exerted by each cell. Instantly, I was convinced, not only that Prof. Abercrombie was correct about the cause of the distortion of the gels, but that I should change my intended research topic and develop flexible gels as a method for mapping the directions, locations and relative strengths of cell forces. He was doubtful if I could get such a thing to work and he would probably have been right if the only purpose of fibroblast traction was each cell's own spreading and locomotion.

I mixed «carbon black» (soot) particles into unclotted plasma, then quickly spread it with the side of a cover slip (the exact way that my mother had taught me how to make blood smears, when I was about 8), so that very thin layers of clot were formed (Fig. 2). When cells were cultured on these layers, time lapse films showed the centripetal movements of the carbon particles, which was a map of the forces exerted. By diluting the plasma with tissue culture medium and then spreading the mixture to form different thicknesses, I could adjust the Young's modulus[1] of my layers over wide ranges. Normal fibroblasts turned out to be much stronger than either epithelial cells or malignant fibroblasts, and macrophages exerted relatively tiny forces and polymorphonuclear leucocytes even less. This range of magnitudes was as much as a thousand-fold. I couldn't figure out what sense this made, but I quantitated the differences by culturing cells directly on the surfaces of liquid silicone fluids. Some had a viscosity of only a few hundred centipoise, others had viscosities in steps up to a million centipoise. The idea was that the minimum viscosity sufficient to support spreading of a given kind of cell would be a measure of the traction forces they exerted. Unfortunately, elastic films of denatured proteins accumulated on these fluids' surfaces, which made their effective viscosity greater than it was supposed to be. Therefore, I repeated the experiments with serum-free medium. These results still indicated that fibroblasts exert forces thousands of times stronger than leucocytes and also thousands of times stronger than needed for their own locomotion.

With Graham Dunn's help, I used polarized light to photograph patterns of birefringence produced by fibroblast traction (Fig. 3). He and I also used tiny particles stuck to cell surfaces to map the patterns of forces exerted and this included both the top and bottom surfaces. At the time, we thought that rearward membrane flow, with membrane assembly along the leading edges, was the most likely method by which the acto-myosin cytoskeleton transmitted traction from the inside to the outside surfaces of the plasma membrane. Graham was collaborating with Adam Middleton on an ingenious method to study contact inhibition.

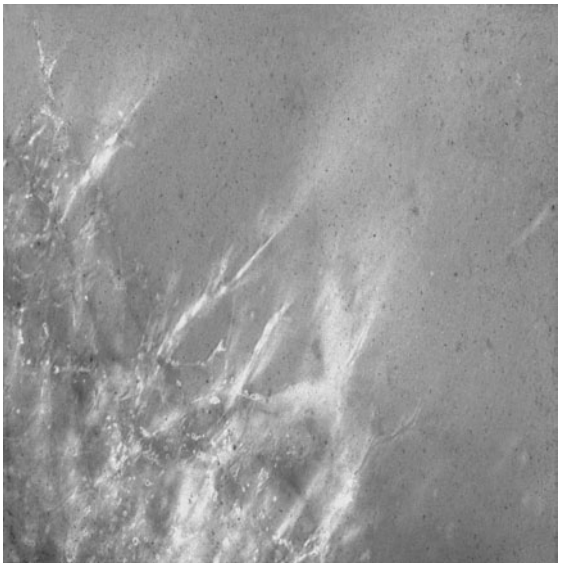

**Fig. 3. Birefringence of plasma clots produced by fibroblast traction.** *Spring 1971, in Michael Abercrombie's laboratory in Cambridge.*

They cultured fibroblasts on commercially-manufactured sheets of silicone rubber, which they then expanded in area by stretching, to measure how much this stimulated cell movement and growth. If I had stayed for a third year in England, surely it would have occurred to one or the other of us to make our own, much thinner, sheets of silicone rubber and use them to measure and map cell traction.

Permanent faculty jobs become available only rarely, especially jobs located where I lived as a child and at the university that I would have attended myself if my father hadn't insisted that I get some experience outside the South. So I flew back to America and interviewed at Duke University and the University of North Caro-

Note 1: "Young's modulus" is a quantitative measure of stiffness of a given elastic material

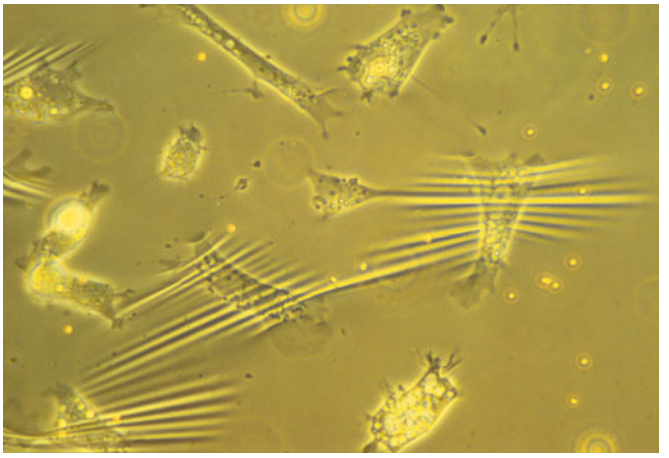

**Fig. 4. Silicone rubber substrata, being wrinkled by fibroblasts.** *The tiny spheres are polystyrene latex particles, used to measure the amounts and directions of displacement of the rubber. (1978).*

lina. I accepted the job at the latter and Duke had a post-doctoral position for my wife in her field of research. And we have been here since 1972, without even any sabbaticals. In 1991 I had the honor to be a visiting professor at the University of California at Davis.

After presenting a paper on flexible gel substrata at a Ciba Symposium in London in September 1972, three days later I was teaching comparative anatomy to big rooms full of undergraduates and nurses in Chapel Hill. The teaching loads here used to be heavier than they are now and the big classes used to be taught by the youngest professors. In 32 years, I have taught about 100 one-semester courses, ranging from the introductory biology course, to human anatomy, to advanced cell biology, but mostly embryology.

For my first 6 years here, I tried to develop all sorts of flexible substrata and used many kinds of plastic as well as polyacrylamide. Even when these methods worked, grant panels and seminar audiences argued that this was only the dehydration shrinkage phenomenon that Paul Weiss had discovered. Every grant proposal that I wrote on that subject was rejected; not just approved without funding, but flatly rejected, in one case after the American Cancer Society had sent a very nice site visit committee down from New York. When I showed them my time lapse movies of the substrata, they assured me I would get the grant; but it was rejected at a higher level, specifically because of that dogma about cells causing gels to shrink and not being able to exert forces.

This was the motivation for trying to cross-link silicone fluids: because they are so biologically inert and not hydrated, so it would be impossible for them to be dehydrated. After trying several chemical catalysts, I resorted to direct flaming of the fluid surface. This worked very well and the method is repeatable, once you get the hang of it. Another good feature is that the rubber layers wrinkle when either compressed or stretched (Figs. 4, 5). Even still photographs convince people that the cells are exerting forces. We submitted this to Science and dedicated the paper to Michael Abercrombie. Several sets of TV news photographers came into my lab and interviewed me and showed time lapse films. It was on CNN and the excellent «Mr. Wizard» children's science show, which had been a favorite of mine when I was a child. My colleagues deserve a lot of thanks for granting me tenure, the year *before* all this, despite rejection of my grant proposals. They had faith in me.

**Why did you then use collagen gels?**

David Stopak wanted to do his Ph.D. thesis on the guidance of nerve axons. Both of us had been strongly influenced by Paul Weiss' idea about tissue organization by whatever phenomenon orients plasma clots. Weiss was wrong about these effects being caused by dehydration shrinkage, but he may have been right about the rest. So David and Pat dissected tendons from rat tails, dissolved the collagen and reprecipitated it to form gels (using the methods published by George Gey and by Bard and Elsdale). Then they plated out small fragments of heart and other tissues, so that fibroblasts would produce Weiss' «Two Center Effect» and David painstakingly dissected out individual nerve ganglia, which he cultured in nearby parts of these gels.

We were disappointed that nerve axons did not orient more in response to these two center effects. But what surprised us even more was that collagen became so strongly and rapidly oriented over such large distances. Two center effects are much stronger in collagen than in fibrin. Collagen lined up dramatically over distances not just of millimeters, but even centimeters (up to six centimeters, which was all the way across the largest petri dishes that we used). While Pat and David were doing these experiments, I was giving lectures on human anatomy to hundreds of students up in the nursing school. Of course, these lectures included tendons, muscles, ligaments, organ capsules, perichondria and other collagenous structures. Eventually, we realized how much the patterns being generated in our collagen gels resembled normal anatomical structures. Therefore, the three of us proposed the hypothesis (which we called «tractional structuring», which never caught on) that the main function of fibroblast traction is alignment, compression and other rearrangements of extracellular matrix, especially collagen. We and everybody else had been studying fibroblasts' locomotion on the assumption that

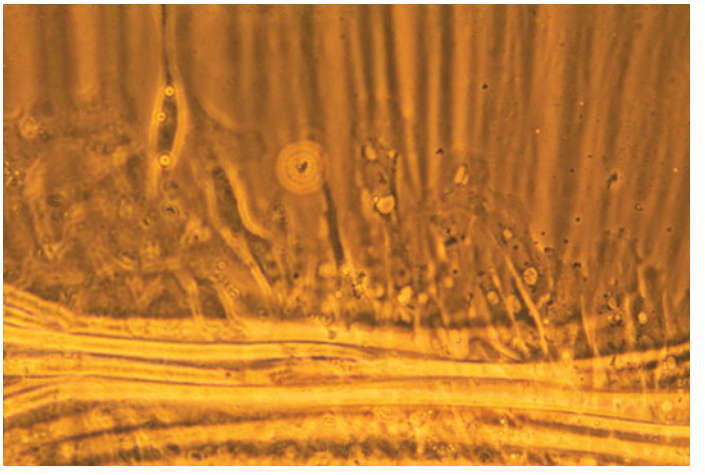

**Fig. 5. Clusters of fibroblasts pull rubber past their lower surfaces, compressing it into accordion-like folds.** *Many square millmeters of rubber sheet can be compressed into the area beneath the fibroblasts. (1978).*

**Fig. 6. A realistic-looking but «artificial» set of bones, tendons and skeletal muscles** *which were generated in organ culture using a gel of rat tail collagen into which were put two cartilages from the leg of a chicken embryo, with separate pieces of embryonic back muscle cells placed in the gel a few millimeters from the cartilages. Traction forces exerted by fibroblasts on certain parts of the cartilage surfaces pulled on the collagen and aligned it to make tendon-like structures, which in turn pulled the muscle cells alongside the cartilages, stretching and aligning them to the shape of normal muscles. When these muscles contracted, they flexed the joint to the angle seen in this photograph.*

it was only a means of getting cells from one place to another. In many other cell types that's true. But what fibroblasts are trying to do is more like a winch hauling in a cable; and that's why fibroblast traction is so absurdly strong. We published this in Nature.

The next stage was when David dissected individual leg cartilages out of chicken embryos, put these next to each other in collagen gels and then plated out fragments of back muscle a millimeter or so distant from the cartilages. If an «elegant experiment» is defined as a crazy idea that works, then this one fits the definition. The results couldn't have been more dramatic. Over six days, traction exerted by perichondrial fibroblasts pulled collagen in toward the cartilages, aligning it into strands connected to the muscle fragments, also aligning the muscle cells and drawing them up against the sides of the cartilages. The result was realistic-looking muscles connected to cartilages by realistic-looking tendons. The collagen was from adult rats and the cartilages and muscles were from embryonic chickens (Fig. 6). Sometimes I wish we had a third or a fourth species, with their cells collaborating mechanically.

David began this experiment the week before Christmas holiday. But the results were so dramatic, none of us could tear ourselves away from what was happening for more than a few hours at a time. Our families had to celebrate without us. The results were our best Christmas gifts that year and made us as happy as children opening presents. After all, embryos have been forming tendons and muscles for a billion years; and we were the first people to realize how they do it. We submitted the results to Developmental Biology and the referees were as enthusiastic as we were.

There were two more sets of experiments in this series. David and Pat tested what would happen if fibroblasts were evenly distributed through a collagen gel, but the edges of this gel were «locked» in position, so that they could not be pulled inward. My only contribution was to figure out how to «lock» the edge of the collagen gel. We used filters made out of glass fibers and punched out large holes in the middle of circular filters, so that just the rim was left. Liquid solutions of collagen were then poured into these doughnut shaped pieces of filter, so that when the collagen gelled its fibers were entangled in among the glass fibers and the rim of each gel was thereby held in place. We used an ordinary «ticket punch» to make the holes in the filter, which turned out to be surprisingly expensive because the store where I bought it was having a book sale! I returned a hour late, with the punch and two sacks of books.

The effect of fibroblast traction on collagen gels whose rims were «locked» in position was to produce alternating regions of compressed and stretched collagen. This was what we had predicted, based on previous observations on pieces of chick embryo skin, in which «feather germs» (equivalent to hair follicles) form by bunching-together of fibroblasts and alignment of collagen fibers between adjacent clusters of fibroblasts. In our artificial system, the clusters of fibroblasts were often surprisingly regular (Fig. 7).

This was at the time (1981) that we had our first «Apple II» computer. The first project on this computer was to produce wave-like patterns by the types of equations invented by Turing and pioneered by Hans Meinhardt (see Interview by Gordon and Beloussov [2006], in this issue). I couldn't see why the two «morphogen» variables should necessarily be chemical concentrations. For example, one variable might be the population density of cells and the other variable might be the amount of tension in collagen fibers. There are no limits on what these variables might be, to generate spatial patterns. They just have to obey one of many alternative sets of equations. You need some elements of autocatalysis, or positive feedback, some elements of inhibition and action at a distance, with one variable acting at

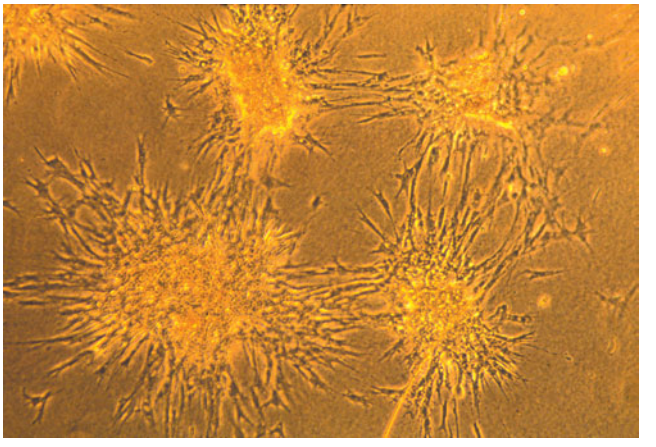

**Fig. 7. When chicken embryonic dermal fibroblasts were trypsinized and suspended in a collagen gel and the margins of this gel were locked in place by a glass fiber mesh, then the traction exerted by the fibroblasts caused formation of regular alternating patterns of high and low cell density, with collagen fibers aligned between the cell clusters.** *This pattern is similar to that of «feather germs» in normal skin and is an example of mechanical forces directly generating relatively large-scale geometric patterns, without the need for either a pre-pattern, a reaction-diffusion system or postional information. Pat Greenwell and David Stopak did this experiment in the spring of 1982.*

longer range than the other variable. Diffusion is just one of many possible ways of acting at a distance and diffusing faster is just one way of acting at a longer distance. More people should write their own computer programs of this kind. I will be glad to send anyone sample programs and am now trying to post some runnable version on the web. Cellular automata are also a good stimulus to think about how complicated but regular geometric patterns can be generated by simple rules; and I do have one of these posted on my web site (thanks to Andy Wheeler, an excellent former student): http://www.bio.unc.edu/faculty/harris/Courses/cellauto.html

The next experiment in this series was the injection of fluorescently-labeled collagen into live, developing chick embryos. These embryos were then allowed to develop a couple more days and then fixed, sectioned, histologically stained and then studied with a fluorescence microscope to determine what had happened to the injected collagen. This was done in collaboration with Norman Wessells at Stanford, in whose laboratory David Stopak did his post-doctoral work. The results were better than we had hoped. Starting out as amorphous gels, the fluorescent collagen got rearranged into different patterns in different embryos. Wherever this collagen got injected, then the anatomical structures formed at that point were made partly out of that collagen, which had become rearranged into the appropriate geometry. Sometimes it got made into parts of tendons, in other cases it got wrapped around blood vessels and in others it had been compressed into perichondria, or woven into the dermis (Fig. 8).

I believe that these results prove conclusively that mechanical forces are exerted on collagen during normal embryonic development and cause it to become arranged into different anatomical patterns. We intended these experiments to disprove both dominant theories: that the geometric arrangement of collagen is caused either by self-assembly (modulated by differences in local chemical environments) or by secretion in place. Neither of those theories could predict our results and I don't know of any published claims that our results can be explained by any other mechanism than the exertion of traction forces, identical to those that we had demonstrated by time lapse photography in tissue culture and in organ culture. Of course, I admit that we had no way to see these forces inside the embryos, while the injected collagen was being rearranged. Now that Green Fluorescent Protein can be intercalated into genes, a good experiment would be to make rats or mice with GFP type I collagen, isolate collagen from their tail tendons, inject this into chicken or frog embryos and use some of the new methods for video microscopy to track collagen rearrangement.

This collagen injection research was published in the Proceedings of the National Academy of Sciences (USA), but only after an eminent collagen specialist made drastic efforts to reverse the manuscript's acceptance. To the best of my knowledge and based on citation index searches, no rebuttal of this paper has ever been published by the advocates of the alternative theories, which continue to dominate the field and monopolize funding. Having failed to block publication of these discoveries, they simply ignored them and continue to write book chapters and review papers as if their theories were the only ones. Further experiments might somehow have disproved our interpretation, or discovered that the true mechanisms work some different way none of us had imagined.

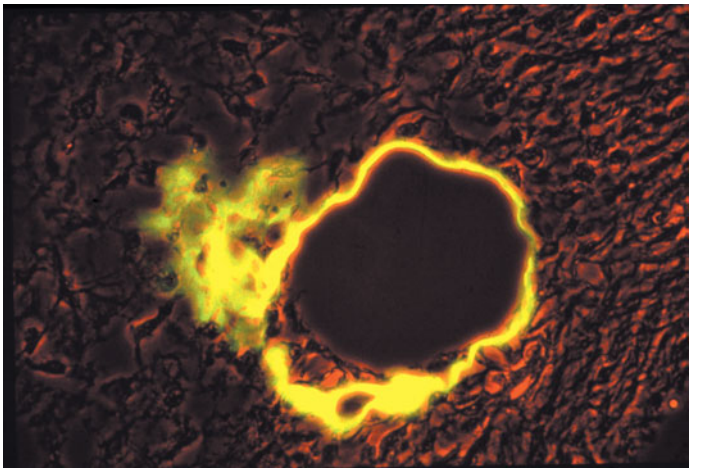

**Fig. 8. When collagen is isolated from rat tendons, covalently labeled with fluorescein and injected into chicken embryos, traction forces rearrange the collagen to form whatever structure then develops at the site of injection.** *This section shows the wall of an embryonic artery, around which injected collagen has been wrapped. David Stopak did this research in the laboratory of Norman Wessells, at Stanford University.*

**The dominant trend in developmental biology could be called «genocentric», in the sense of expecting to explain embryonic events only in terms of the genes that «control» them. What is your opinion?**

My concept of embryology is a bridge to connect genes to anatomy. Continuity is crucial. To concentrate on one end or the other is a way of avoiding the most difficult and interesting parts of the problems. It is just as misguided as it would be for bridge-builders to put all of their effort into one end of a bridge, at the expense of the middle.

Even when a gene controls, for example, the location or attachment sites of a muscle, the gene can only produce these effects by adjusting mechanical forces exerted by and on cells. So the question is not whether causation is by genes or by mechanical forces. The real question is how genes create and control forces so as to produce different anatomical structures.

Movements and rearrangements cannot be caused to occur except by physical force. Embryology is a complex sequence of cell rearrangements. Gastrulation requires forces; neurulation requires forces, somite formation requires forces; the subdivision of somites into dermatome, myotome and sclerotome requires forces; the migration of muscle cells requires forces. My molecular biologist friends prefer to believe that these forces only come at the end of the causal chain farthest from the genes, so that it is more important to identify which genes will result in abnormalities in which organs when mutated and which genes code for receptors for a given family of signalling molecules. When they have discovered enough details about genes and protein structure, then they expect the rest of embryology to fall into place. They also like to use the word «information» in ways that convey no information, such as «These genes provide the information to make blood vessels.» The «blueprint» analogy is also very

popular. Some of this is selfishness and much of it reflects the reality that humans build things almost entirely by imposing external forces on materials. If we had more experience causing structures to build themselves by adjusting the mechanical properties of the component materials, then gastrulation would make more sense to us.

I believe that if David, Pat and I had reported evidence for something like chemotactic attraction of muscle and tendon cells to their sites of attachment - a chemical mechanism instead of a physical one - then our grant funding would have had a much better chance of being renewed. The panels' repeated criticisms were that we should be more molecular. Forces are «descriptive», while genes are «causal».

Ironically, when my wife and I were undergraduate students, the biases we faced were in the opposite direction. Things have changed there and the college we attended now has on its faculty the author of the best English language textbook in developmental biology. Earlier editions of this book included some of my discoveries about mechanical aspects of development. This has now been pushed aside to make room for a flood of what I admit are very interesting and important molecular discoveries. There is nothing at all about the mechanics of development.

When we were students, the biology department at that college refused to teach any biochemistry, cell biology or molecular genetics. A few students protested this, led by my good friend Stanley Adamson and my future wife, Elizabeth Holder (but not me). Their protest was of such an admirable kind, it deserves to be remembered; they organized what might later have been called a «teach-in». They reserved a lecture hall for a Saturday (in the chemistry and physics building, because the biology chairman refused the use of their building) and 6 or 7 students dressed up for the occasion and each gave a half-hour lecture on recently published research in the molecular subjects that were not being taught at this college. They showed by example what their professors should have been including in their lectures. All students and faculty were invited to attend and most science professors did attend, but nearly all the biology professors boycotted it.

These disputes altered my life drastically. In order to be with my friends and especially with my girl friend, I had to take as many advanced chemistry courses as I did biology courses. Among other things, this meant a year of thermodynamics. My chemical training is as solid as any molecular biologist I ever met; and my titrating skills are unsurpassed, especially for a herpetologist. In my debates with Malcolm Steinberg and his students about the mechanism of cell sorting, they have accused me of «not understanding basic thermodynamics». If they only knew!

To conclude this story, the biology faculty resented this teach-in so much that they counter-attacked in ways that would eventually make them ashamed enough to be willing to change. Every student had to pass a comprehensive exam to be able to graduate. This exam had always consisted of many questions from different areas of biology and was intended to test breadth of knowledge. First came a long written exam, followed two days later by an oral exam by the whole faculty. Stanley and Elizabeth were in different academic programs and were therefore not subject to this exam. But I was. To teach us their power and contrary to all tradition, the biology professors made that year's comprehensive exam consist of only one question: which was to «explain why thermodynamics does not apply to living things.» Part of my answer was that this is no more true than that gravity doesn't apply to birds. On the cover of my answer booklet, I complained to them that it was immoral to force students to pretend to agree with controversial opinions about which the department chairman was known to hold extreme opinions.

To everyone's surprise, the biology faculty voted to refuse to me an oral exam, thereby preventing me from graduating. Such a thing had never happened before, or (I hope) since. Among the effects was that the Dean realized that maybe there was some truth in all those complaints they had been getting for years about the biology chairman and his biases. It helped that I had gotten some of the highest scores on the «GRE» national exams and was generally known for having a broad knowledge of biology (then as now). So there were investigations and eventually the biology chairman was removed from his position and new hiring policies were begun that brought molecular biology into that department for the first time. It became a balanced department and did not swing to the opposite pole. By the time I got my diploma, I was well along toward getting a Ph.D. from Yale, in their Developmental Biology program, where the comprehensive exams included molecular biology and where I passed them a year earlier than required.

**What is your opinion about the roles of physical and engineering approaches in analysing embryonic development? How can those approaches be coordinated with more conventional ones, based mostly on chemistry?**

My opinion is that discovering embryological mechanisms is equivalent to «reverse engineering» of an alien technology. Imagine that an alien space ship had crashed on the earth and we were trying to figure out how it worked. What we learned would eventually help advance human engineering methods; but meanwhile our perceptions of the alien machinery would tend to be biased toward our expectations that the aliens would solve problems in the same ways humans do. Among such biases, the strongest is that humans build things by imposing exterior forces on materials, instead of by adjusting the internal properties of the materials so that they will spontaneously shape themselves. I believe this bias is one of the main reasons that so many people prefer to think of genes as blueprints of anatomy, somehow directly causing tissues and organs to develop their proper shapes, instead of being concerned with what forces the genes have to adjust in order that these shapes will form spontaneously. Architects need not be too concerned with the details of bricklaying, or pipe-welding. Or perhaps genes are thought of as deities: «Let there be a muscle at a certain position; And there is a muscle!»

The causation of anatomy by genes always includes forces of some kind. In principle, cell differentiation could be controlled spatially such that each cell type would form at its correct location and then stay there, with minimal geometric adjustments perhaps being caused by different amounts of growth. Embryos that developed that way would have no gastrulation, no neurulation, no neural crest, no somites, no myoblasts migrating into the limbs. A human engineer, who had never learned much actual biology, or didn't care about the truth, might reasonably guess that development is just a matter of signalling to each location which cell type should differentiate there. He might even convince

geneticists that this is the most fundamental way to think about embryonic mechanisms, that they are all a matter of signalling cells what to do. Most geneticists might be happy to believe this and also to believe that this was a profound insight. Others would regard such an approach as a tautology, equivalent to saying that differences in cell behavior are caused by whatever signals cells how to behave. In fact, what saves it from being a tautology is that it is factually wrong most of the time.

Chemistry has contributed toward controlling the strengths and properties of materials used in engineering (plastics, alloys, semiconductors), but has rarely tried to create macroscopic shapes. Crystals are one example in which chemicals create shapes; D'Arcy Thompson collected examples of biological shapes that could be created by simple sets of forces; and Turing invented a combination of reaction and diffusion properties that would be able to generate wave like patterns. We can go much farther in these directions. A very economical method to create an eyeball is to have an internal fluid pressure, pushing out equally in all directions at each point and being resisted by a constant amount of tension over most of the periphery of the eyeball, but with this tension adjusted to a lower amount in the disc where the cornea is. Of course, from teaching embryology, I am very much aware that the different parts of the eye have separate origins. The contractile tensions in the cornea and sclera are what I suggest create the surface curvatures. The shaping of cartilages depends on relative amounts of tension in collagen fibers on the cartilage surface and also within its interior.

We can also go much farther in the direction of chemical reaction-diffusion systems. In particular, the interacting variables do not need to be chemical concentrations and their «diffusion rates» can be replaced by other kinds of action at a distance. One variable could be mechanical tension and the other could be the local population density of cells. Having one «morphogen» diffuse faster than the other is just one of many alternative ways to produce longer-range effects. The morphogen variables themselves can be tensor variables, like mechanical stress, or could even be elastic moduli. As soon as I first started writing computer programs that obey Turing-like sets of rules, it was quickly obvious that the variables and their effects could be almost anything. The question is to find out what embryos actually use and there is no particular reason to believe that these variables are concentrations of diffusing chemicals.

Engineering makes good use of «finite element simulations», that are designed to predict the mechanical distortions of pieces of metal, concrete or other building materials, when these materials are subject to loads. The elastic moduli, breaking strengths and other properties of the building materials are programmed into each simulation and the goal is to find out whether it will break under a given load, what the maximum breaking strength should be and where the break is most likely to occur. The assumption is that the forces come from the outside in. Biologists can write their own finite element simulations, as I and others have, in which the internal properties of the materials can be continuously adjusted, at will, for example by using the computer mouse. The goal is to study morphogenesis from the inside out, by discovering combinations of physical properties that are sufficient to cause something like a cartilage to swell spontaneously to a given shape observed in embryos. Then the real embryonic cartilages or other structures can be examined to find out whether their strengths and spatial distributions match those in the computer simulation. Computer simulations can be used experimentally, to compare the predictions of alternative theories about forces in cells and tissues. Using this approach, Sally Gewalt and I tested alternative theories about the induction of the contractile ring in cytokinesis. In that subject, there has long been debate between «polar stimulation» and «polar inhibition» theories and our simulations showed that both alternative theories make several testable predictions that no one had previously noticed. For example, if a cell is squeezed into a conical shape, all workable stimulation theories turn out to predict that the contractile ring will form nearer the narrow end of the cell; and all inhibition theories (without the advocates of these theories having noticed it) predict the opposite, that the cleavage furrow should develop nearer the broader end of the cell. Ray and Barbara Rappaport then did this experiment and the results matched what the computer program predicted should happen if the signals from the mitotic poles act by strengthening cortical contractility of the cell.

**Do you think that developmental biology should move toward becoming a more physical science, in the sense of developing theories with strong predictive powers? Or is this goal so impossible or needless that our science is doomed to rest as a set of more or less isolated facts to be memorized?**

I believe it can be made into a much more predictive science than it is now, especially if it borrows concepts from Economics, as well as Bioengineering. Since Adam Smith, David Ricardo and also Marx, economists have developed conceptual models of society that are based on balances between supply and demand and other pairs of variables. This line of thought has become extremely sophisticated, although its predictions are not always quite correct. Many excellent embryologists try to use the concept of minimization of thermodynamic free energy to make sense of phenomena in which cells spontaneously arrange in some particular pattern. But that concept only applies to a narrow range of phenomena in which all the forces are conservative and do not expend energy in a state of balance. Economic equilibria would be a much more useful analogy, because they can depend on all sorts of counter-balanced tendencies. Historically, the governments of some countries have controlled their economies by adjusting variables such as interest rates, tariffs and other taxes. Other governments tried to enforce the end results, rather than to manipulate the rules so that these end results would occur spontaneously. It is ironic that so many people, especially those coming from backgrounds in genetics or engineering, should assume that genes cause the formation of anatomy by dictating the results, instead of by manipulating rules of interaction. One of the great advantages of this latter approach is that balances between opposed forces can often optimize the end results. In economics, this is a basic principle. This analogy to economics was first pointed out to me by David Stopak, who had been a double major (Biology & Economics) when he was an undergraduate.

Bioengineering, in contrast, focuses on those aspects of anatomy that seem to be approximately optimal solutions to engineering problems. The tacit assumption is that this optimization results from evolution, in the narrower sense of many alterna-

tive geometric arrangements having been tried out, with natural selection favoring genetic «blueprints» for optimal structure. My suggested alternative is that evolution can also yield mechanisms of structure creation that themselves optimize the geometry of the structures they produce. For example, «Murray's Law» is a combination of properties observed in the relative diameters and branching angles of arteries. Should we believe that evolution has produced combinations of genes that dictate the specific paths and diameters of arteries in our anatomy, in the sense that a blueprint would specify the paths and diameters of pipes in a building to be constructed? An alternative is that genes cause cells to obey what amount to algorithms and that the outputs of these algorithms are functionally optimal geometric patterns, whether of arteries or anything else.

**As a university professor, are you satisfied by the structure and the level of education in fundamental biology? Do you think that emphases should be changed, or not? Are your students interested in problems of fundamental science? Can you discuss your own research interests with them?**

I am frustrated that people think of biology as being inherently less conceptual than physics or chemistry. Every time I teach introductory biology, I try to make the content as conceptual as a good physics course would be and more conceptual than chemistry. I admit that biology has a large component of phenomena that happened to evolve one way and could in principle have been otherwise, as is also true in geology and astronomy. There is still enough of the herpetologist in me that I secretly treasure weird creatures and phenomena. But concepts and principles are even more interesting and the courses we teach should emphasize this.

My students are fascinated by the prospect of fundamental improvements in medicine, resulting from better understanding of the mechanisms that create and maintain anatomical structures. Blood vessels are an excellent example. Until we understand the mechanisms that build them in the first place, then how can we expect to understand what goes wrong in atherosclerosis, aneurisms, varicose veins, etc. We are held back by the concept of genes as blueprints, that dictate structure *from the outside in,* with the result the medicine has no better solutions than grafts, bypasses and transplants.

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