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"What price intellectual honesty?" asks a neurobiologist

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Career

I was born in London, although both of my parents went to Scottish Universities. I was brought up to respect academics, and to believe that their paramount interest in life was the pursuit of truth. My intention had always been to take up a career in a university, in which — as long as one carried out the teaching duties assigned by the head of department — one was free to do research in any area in one's discipline, which seemed exciting. At that time in Britain academics were protected from those with orthodox opinions in power by long established tenure.

I obtained a scholarship to University College School, London, and took a medical degree at Middlesex Hospital Medical School in 1956, since when I have practiced as a part-time physician. I proceeded to a degree in neurophysiology and biophysics at the Department of Physiology, University College, London, and completed it in 1958. I also obtained a diploma in biophysics from Kings College, London.

I then went to the Institute of Psychiatry, first as a research assistant and then as an Honorary Lecturer in Biochemistry, and I stayed there until 1962. I was working on the electrical properties of slices of brain, and was invited to examine similar properties of nerve cells dissected out by hand, in Sweden. I returned to Britain in 1964 and took up the position of Biochemist and Honorary Lecturer in Applied Neurobiology at the Institute of Neurology in London. The following year I was appointed Senior Lecturer in Physiology at Battersea College and, in 1968, I was made a personal Reader in the University of Surrey. I was in charge of all physiology teaching in the University at that time, and have been the senior physiologist since then. In 1970, I set up the Unity Laboratory of Applied Neurobiology, which I have directed ever since. I have published about 150 full-length publications in cytology, neurobiology and resuscitation, and have written five books.

Throughout my career, my upbringing and training led me to entertain the following assumptions: academics' first priority is to seek the truth as they define it; they are prepared to enter into dialogue about their beliefs and research; they believe that evidence and reasoning should take precedence over belief and emotion; they behave fairly in argument; they do not practice casuistry; and they do not use power to defend their views. I have reluctantly come to the conclusion that these assumptions are not always warranted.

A student of the Institute of Psychiatry, 1958-1962

My first job in 1958 was as research assistant to Professor Henry McIlwain, at the Institute of Psychiatry, London. He was the most active exponent of the use of thin slivers cut from brain for the study of the biochemistry and physiology of the intact living brain. I believe that he had learnt the technique from Professor Sir Hans Krebs, the Nobel Laureate in biochemistry, with whom he had worked in Sheffield, England. The properties of the brains of adult animals could be studied in slices for up to two hours before they degenerated. Professor McIlwain had built up the Department of Biochemistry with a small nucleus of permanent staff, and 10-15 visiting

research workers and students for doctorates of philosophy.

At the Institute of Psychiatry, I became aware of certain fairly common practices. Some people did not quote authors they did not like personally, or others who had predated them, or had findings that senior staff did not like. They would fail to do control experiments or would discard results which gave different results from those they expected. When I first heard about these practices, I was shocked by them, but I was even more shocked by the tolerance and cynicism which some of my colleagues displayed towards them.

In 1958, I was discussing a particular biochemical problem with a senior Hungarian biochemist, who came to the Institute legally before the Revolution and had applied for asylum in Britain. This was granted on condition that he remained in the same position. He told me that he quite agreed with me, but would not say so in public, as it might risk his appointment here.

I devised a simple technique for cutting slices quickly, so that they could be studied sooner than by the previous technique. One of my colleagues liked the idea, and was put on to the task of studying the properties of slices cut in this way. We worked harmoniously together, until one day he stopped coming to my laboratory, and I noticed that he was avoiding me in the corridor. A senior colleague had ordered my friend to work with him rather than to develop my technique, but I was too junior to be able to protest.

I heard along the grapevine that this senior colleague was writing up a paper based on my work, and when I asked if I would be a co-author, I was told that my help would be acknowledged. In the event, when the paper appeared, I noticed that it ended with an acknowledgement for my "help" with the technique, but I had not been asked to be a co-author.

When I read the published paper, I noticed an important mistake in one of the calculations. I pointed this out politely, but I was told that it was just a different way of expressing the value. No, I maintained that this was not true, because a similar constituent had been calculated correctly, and the result reported was in impossible units.

This mistake, once published, became the correct values, and later publications showed similar ones. In a book written later, different pages show different values for the same parameter. The book is very authoritative. I did not wish to hurt the feelings of those responsible, but when I wrote a paper subsequently on the same subject, I inserted the correct calculation; there was some difficulty in publishing it.

I learned several lessons from my time at the Institute of Psychiatry. Firstly, doctoral students have no redress against their supervisors, since their careers would be ruined if they made determined criticisms, or resigned their studentships. Furthermore, well-known academics find it relatively easy to publish in a journal, especially if they are on the editorial board. Thirdly, the data reported in weighty books acquire an authority and inertia, which encourages some other people to find similar results, and dissuades others from submitting different results for publication. This was my first personal experience of misdemeanour, and it disturbed me greatly.

Research Fellow in Göteborg, Sweden, 1962-1964

In 1962, Professor Holger Hydén, at the Institute of Neurobiology, Göteborg, invited me to do similar studies on single nerve cells dissected out by hand from the brains of freshly killed rabbits.[1] The technique is brilliant in its simplicity, and is not difficult.[2] A large number of experiments were carried out on the biochemistry and anatomy of the cell bodies, but the same question was asked, as had been asked about cerebral slices. How many of the electrical properties of the living nerve cell survived its separation? I was employed with many others to find out.

I had a very interesting and fruitful time at the Institute of Neurobiology under Professor

Hydén, who was very kind to me personally. However, I saw there two practices of which I had been previously unaware. A technician would produce a table of results, and the supervisor would strike out some of them, without giving any reason for so doing; the technician then retyped the table, discarded the original, and the new table became the raw data. In recent times in Britain, I have seen research workers simply deleting values from the computers attached to their instruments. I do not believe these practices are widespread in Sweden or in Britain.

The real worry was that such selected and, therefore, misleading data should occur in published papers, and then become part of the canon of knowledge. In the real world, the idea that they would be corrected when other people tried to reproduce the experiment is just wishful thinking. As a consequence of these observations, I made the decision that I would never myself indulge in, or put my name on publications, in which I knew that manipulation of results or intellectual casuistry had occurred. During the next few years, I identified a large number of widely practised and tolerated misdemeanours, such as not discussing results which disagreed with one's own, avoiding doing crucial control experiments, answering important questions with artful circumlocutions, etc.[3]

Adenosine triphosphate (ATP) is one of the most important chemicals in the body. It is required for many metabolic reactions and it helps to synthesise proteins. Its energy is used to move water and it causes muscle to contract.

An American research worker visiting Göteborg, Dr. Joseph Cummins, developed with Professor Hydén a method for measuring in single nerve cell bodies[4] the activity of the enzyme ATPase which breaks down ATP; these cell bodies had diameters of a fifteenth to a thirtieth of a millimetre; this was a very significant achievement, and we were able to modify the technique and find much more enzyme activity.[5] The experiment involved measuring very small concentrations of ATP, so I wondered if one could measure the change of this 'high-energy' compound in retina (part of the eye), composed of thousands of cells, when light was shone on to it. I found a considerable change. Since the retina is an outgrowth of the brain, I sought the same effect in slices of brain, spinal cord and the sciatic nerve (which runs down the back of the leg), and found that all these tissues exhibited it. Then I asked myself, "Why should one have a light-sensitive enzyme in the nerve upon which one sits?" After 3 months of intensive experiments; I left out all the tissue. To my astonishment, the ATP itself was sensitive to light. This was unexpected and had not been reported before. I repeated the experiments with a much *less* sensitive method of measuring phosphate.[6] The results were the same.

I have always been of the opinion that when a humble journeyman of a research worker finds something exciting about such an important molecule, it is likely to be either a mistake or an artifact resulting from the procedure. All living tissues employ complicated and fragile biochemical mechanisms. Most experiments involve killing an animal or plant, arresting change within it (fixation or inhibition), spinning it, freezing it or adding powerful reagents. Any of these stages of a procedure can and often do change the biochemistry of the tissue drastically, or relocate particular chemicals within it. Therefore, biochemists have to demonstrate unequivocally that any effects they find arise from the innate properties of the tissues, rather than from the procedures used to examine them. Experiments to test the effects of the procedures themselves are known as 'control' observations, and the fundamental validity of any experiment designed to find out what happens in the intact human being, animal or plant, is largely determined by the care with which the controls have been carried out. Popper[7] told us that one should try to falsify one's own hypothesis with relevant 'control' experiments.

So I embarked on a long series of control experiments, testing the effects of light on

compounds allied to ATP, including ADP, AMP, and inorganic phosphate; I tried the effect at 22ºC rather than 37ºC on ATP; I washed the glassware with detergents not containing phosphate; I took out the oxygen. None of the other substances showed the light sensitivity of ATP, which required oxygen, and occurred at body temperature, but not room temperature.

I made extensive literature searches and could not find previous reports of this finding. One day, my technician, Miss Anita Bäckman, was away, and I was making up the solution. I took the bottle of ATP out of the refrigerator, and noticed that it was labelled, 'keep cool, in the dark.' So I wrote to Dr. Berger, the chief chemist of the manufacturer, Sigma, to ask if he knew of any publication of this phenomenon. He replied that his company had found it by accident, because it had been despatching chromatographically pure ATP from the United States, but customers in Europe had complained that they were receiving mixtures of ATP and its breakdown products, ADP and AMP. When Sigma put the ATP in dark bottles, it did not break down spontaneously. The company had not published the finding. However, I felt reassured by the knowledge that someone else had previously and quite independently detected ATP's sensitivity to light.

ATP used to be regarded as a 'high energy' phosphate,[8] until the concept was reexamined[9] and it was also shown to be completely wrong by the redoubtable Dr. Barbara Banks, who had great difficulty in publishing these views.[10]

One day, Miss Anita Bäckman, Miss Inger Augustsson and I were sitting in the warm room at 37ºC with the lights turned off doing an experiment. It was necessary to study light sensitivity in the dark. We were talking to relieve the boredom of waiting for 20 minutes. That evening, when I analysed the results of the experiment, it became clear that some agent in addition to light was having an effect. Virtually the only explanation was that the talking altered the stability of the ATP. I sought a source of sound, rich in high frequencies, and used some recorded bagpipe music. We started doing experiments early in the morning in the warm room, close to the entrance of the Institute. By coincidence, members of staff coming to work passed the door and heard the bagpipes, which they thought I was playing to the two young ladies. The bagpipe music had a considerable effect on the stability of the ATP, so we tested pure notes at different intensities, and different frequencies at the same intensity; they all showed that at 37ºC, ATP was sensitive to sound. We subsequently showed that it was also sensitive to spinning in a desk top centrifuge at 1000 rpm for 5 minutes, electric current induced from a loudspeaker coil, and different concentrations of sodium and potassium ions in the range of concentrations normally found in the body.

ATP provides the immediate energy for muscle contraction,[11] but energy is stored in muscle as creatine phosphate,[12] and the 'high energy phosphate' of cold-blooded animals is arginine phosphate.[13] So we repeated all the experiments we had carried out on ATP on creatine phosphate at 37°C, and arginine phosphate at 23°C. They all showed the same effects. Between 1962 and 1964, we did each experiment at least six times, and the analyses were made at random, the technicians not knowing when they measured the samples whether they were control or experimental, or when they had been extracted. We did about 70 experiments *before* we were satisfied that the technique[14] was as sensitive as we could make it, and then carried out over 330 further experiments for publication.

Return to Britain: the Medical Research Council Unit of Applied Neurobiology, London, 1964-1965

Light, sound, centrifugation and electric current and physiological concentrations of sodium or potassium ions, all affected the stability of the three phosphates. Each of the

six different kinds of energy could be transduced or converted into chemical energy for metabolism, so in 1964 I wrote a paper entitled, 'The phosphate bond as a transducer.' It was a tactical error to mention a hypothesis in the title, and also to include the experiments on bagpipes, as this enabled referees to trivialise them. I submitted the paper for publication to the *Journal of Physiology*, whose referees said that my reagents ATP, creatine phosphate and arginine phosphate were not of the highest purity obtainable; I answered that such naturally occurring substances were not pure in living animals. The journal *Nature* said it had no room. The *Journal of Molecular Biology* gave no reason for rejecting it. The *Biochemical Journal* wrote to me that the idea "that physical agents could have biochemical effects was revolutionary." I replied that, on the contrary, it had been concluded that physical agents could have chemical effects, when Count Rumford at the time of the French Revolution showed that boring canons generated a great deal of heat. It became fairly clear that the journals did not wish to publish my paper. The referees did not like the findings, perhaps because they felt threatened by them, but I have never found out why.

Professor Hans Krebs — the Nobel Laureate in biochemistry — wrote to me that he thought a journal had the right to refuse to publish a paper if the referees *thought* that there was something wrong with it, but could not identify the error; I respectfully disagreed. Professor A.V. Hill — the Nobel Laureate in physiology — agreed that the effects had probably been demonstrated, but he could not recommend a journal which would publish the manuscript. Sir Ernest Chain, whose method[15] I had modified, agreed that the modification was reasonable, and that I had, in fact, demonstrated the effects we claimed. Dr. Isaac Berenblum also agreed that we had modified his technique[16] suitably, but he would not comment on the experiments, as his field of research had moved to cancer.

In 1964, I presented my findings at the International Union of Biochemistry in Washington, the (British) Biochemical Society and the Physiological Society, in order to hear any new criticism, and to create a better climate for publication of a full paper. At the two biochemical meetings, the audiences made humorous or sarcastic comments, but very strange events occurred at the Physiological Society Meeting in Mill Hill, London, in November 1964.

About a fortnight before the meeting, Professor Max Born, of the Department of Pharmacology of the Royal College of Surgeons, asked me to come over to his laboratory to set up the ATP experiments which I was going to report. I had just done the first two experiments to set up the procedure. These were not accurate enough to give reliable results. He then told me that he had wasted enough time and he wanted to stop doing them. I told him that I did not think this was fair, since I had done over 70 experiments in Sweden before I was satisfied that the reliability was great enough to start a substantive series.

I was then the second most senior worker at the Medical Research Council Unit of Applied Neurobiology at the Institute of Neurology in London. The Director was Dr. John Cavanagh. He heard about my proposed paper, and said that someone — whom he refused to name — had told him that my paper would meet much opposition at the Physiological Society, and I would be wise to withdraw it. He would not say on what grounds it was to be attacked. His concern seemed so strong that I offered three times to withdraw it if he were to say that my presentation would damage the reputation of the newly formed unit. No, he insisted, that I had the right to present it, but still he advised me strongly against doing so.

Dr. Olof Lippold, the Reader in Physiology at University College, had agreed to introduce my paper, since I was not then a member of the Society. He also told me that I was going to be attacked by Professor Born, who sent me a summary of what he was going to say. I told

Dr. Lippold that I believed that I had precise answers to any questions, including Professor Born's, which were likely to be raised.

Before the meeting, Dr. William Feldberg, the chairman of my session, said that he had heard that my presentation would be strongly attacked, and probably refused publication. This could happen by a simple majority of those who chose to vote, and would damage my career seriously. He even offered to say that I was not present, which would defer my paper to the next meeting. Knowing that Professor Born was to lead the attack, I offered to defer giving my paper if those who did not like it were prepared to try to repeat my experiments. I received no such undertaking.

As soon as I had finished my ten-minute presentation, Professor Born rose and showed one of the two experiments I had done in his laboratory. He asserted that since *these* two experiments had not shown a significant effect, those from Sweden I reported were not significant either. I answered that I did not see how only two experiments with 300% error could be used to invalidate about 330 with only 0.3% error. Professor G.S. Brindley said that I had not shown the effect of shining light on inorganic phosphate, or *not* shining light on ATP solution. I replied that these had been my first two slides. I was asked if I had used spectroscopically pure reagents. No, I answered, but the 'high-energy' phosphates were chromatographically pure. Had I tried the effect on ADP and AMP? Yes, I said, and the effect was not there, as I had said in my presentation. I was satisfied that I had answered every question fully and without equivocation.

I counted about 200 people in the audience, of whom some were visitors. About four voted in favour of publication, about 15 against — the rest abstained. The abstract was not published. Professor Born came up to me to say that he was sorry that my paper had been rejected. I did not answer him. Professor John Butler of the Chester Beatty Institute said that I would probably not now be able to find a job in physiology in Britain. My director, Dr. Cavanagh, said that he had heard that I had "made a fool of myself," and that the Medical Research Council did not like my research. I replied that before taking up the job in his unit, I had listed the experiments I wanted to do, including those on 'high-energy phosphates.' I requested to discuss this opinion about my experiments with those members of the Medical Research Council who did not like them, but he would not tell me their names or arrange a meeting.

The Physiological Society Meeting taught me something. Eventually I published the effect of light on ATP,[17] but not on creatine phosphate or arginine phosphate, nor the effect of light, sound, centrifugation, electric current or sodium and potassium ions in the natural concentrations found in living tissues on creatine phosphate or arginine phosphate. However, a short report appeared,[18] and the full text was circulated by the Information Exchange.[19]

Some years earlier, the American, Dr. B. Chance,[20] the Russian Dr. S. E. Shnoll and collaborators[21] and a Dutchman, Dr. F. A. Hommes,[22] had shown similar effects, so I wrote to each of them privately to ask if they had ever observed the phenomena I had seen. None of them answered, so I asked them through the Information Exchange,[23] but none of them replied. Their findings supported mine, but I still failed to obtain full publication in a refereed journal. My experiments remained suspended in an agnostic limbo, and my career was at risk.

Subcellular fractionation

In 1964 in Göteborg, I started looking into the theory of the effects of light, sound, electricity and centrifugation. The latter was of particular interest, because centrifugation was so widely used in subcellular fractionation. Usually, when biochemists, biophysicists, cytologists, pharmacologists or oncologists tell one what happens in, say, the nucleus, the cytoplasm or the membrane of cells, they have used the procedure of subcellular fractionation. This is

intended to separate a fraction believed to be particularly rich in that part of the cell, so that its unique biochemical properties may be examined separately. The steps of the procedure are listed in the next paragraph. All experimental procedures used in the sciences imply necessarily the *assumption* either that the procedure itself does not change the biochemistry of the tissue being studied to a greater extent than the changes claimed between the control and the experimental tissues, or that any changes produced are too small to affect the result of the experiments. Does the final material extracted reflect the properties of the living tissue from which it came?

I used the following approach. I made a list of the steps of the procedure: for example, the animal is killed; it cools down; a particular tissue, such as the liver, is excised; a strong reagent is added to facilitate homogenisation (mashing up); the tissue is cooled; it is homogenised; it is cooled again; the homogenate is centrifuged (spun round rapidly); fractions each believed to consist largely of a particular cell constituent are separated and frequently washed; substrate mixtures are added; the product is coloured, so that the intensity of the colour read on a spectrophotometer tells one the rate of a reaction in a particular part of the cells. Of course, there are numerous variations of this procedure.

Having identified the steps, I sought in the literature findings indicating the extent to which each of the steps of the procedure could change the properties of the part of the cell, its distribution or activity. I then listed the assumptions built into the procedure, which had to be true if the properties of the cells were to reflect those in life. Finally, I listed the minimum control experiments which might satisfy one that measurements at the end of the long procedures reflected the original properties of the living intact structures.

The assumptions inherent in a procedure are crucially important, since, like a chain, the validity of a whole experiment is dependant on the strength of its weakest link. When I first examined subcellular fractionation,[24] I identified 15 assumptions, some of them contrary to the laws of physics and thermodynamics; the second time I looked, I found 24 assumptions.[25] Other biochemists might deny that some of these assumptions were inherent, or they might add others, but, with one exception, they have not done so.

In 1972, I first raised the question of control experiments to test the effects of procedures on the final results of experiments.[26] It seemed that no one had done these, and this meant that the experiments were incomplete, and that conclusions could not be drawn from them, nor could theories be derived from the conclusions. My uncertainty about control experiments led me to write to the (British) *Biochemistry Society Bulletin*,[27] asking whether any biochemists knew of any published references that control experiments on the effects of the procedures on the results of experiments had indeed been done, or they would say that these were not necessary. There was no answer to these questions.

Other procedures widely used in cytological research

I was so disturbed by the thought that subcellular fractionation might be an unsatisfactory technique that I decided to take a completely different technique and subject it to a similar analysis. I took electron microscopy, asking the question, 'How much does a picture taken with this instrument tell one about the structure of the living cell?' Since the early 1950s, there has been a passion for relating 'structure' to 'function,' that is, the appearance by electron microscopy of a particular identifiable part of a cell with the biochemistry it exhibits.

The light microscope had been used to examine living cells, unfixed tissue and stained sections for 100 years until the 1940s. At that time, the electron microscope was introduced. It permits much higher resolution and magnification than the light microscope, but the tissue can not survive the low pressure, the bombardment of electrons and x-radiation

in the electron microscope, so it has to be coated with a deposit of salts of osmium, lead or tungsten, which is not destroyed by these agents, and can therefore be examined. Cytologists were very anxious to use this more powerful instrument to look at the fine structure of cells.

Science is so complex nowadays that frequently research workers have to resort to evidence derived by other specialists using techniques those citing them do not understand. They assume that their colleagues perform careful and valid experiments, whose fundaments have been examined adequately. My experience is that this is not always the case. I believe that a proper philosophy for scientists is that they should understand *all* techniques whose results they use or quote. They should be prepared to examine criticisms of findings they use as evidence in case their invalidity would throw doubt on the conclusions derived from them, and their value as evidence in other fields. Since truth should be universal, all scientists have a duty to resolve all anomalies and inconsistencies not only in their own beliefs but also in those they quote, and between their findings and those of other workers using the same and different techniques.

Unfortunately, electron microscopy was even more questionable than subcellular fractionation. So was histochemistry (the study of tissue sections), which I chose to analyse because it was somewhere between subcellular fractionation and electron microscopy. I then took three techniques nearer the measurement end rather than the preparation end of the former techniques: these were chromatography, electrophoresis and radioactive measurements. Each of these had their burden of assumptions, many of them evidently unwarranted.[28]

For example, most cytologists know, but readers of elementary textbooks do not, that when one looks at an illustration of an electron micrograph: an animal has been killed; it cools down; its tissue is excised; the tissue is fixed (killed); it is stained with a heavy metal salt; it is dehydrated with increasing concentrations of alcohol; it shrinks; the alcohol is extracted with a fat solvent, propylene oxide; the latter is replaced by an epoxy resin; it hardens in a few days; sections one tenth of a micrometre thick, or less, are cut; they are placed in the electron microscope, nearly all the air of which is pumped out; a beam of electrons at 10,000 volts to 3,000,000 volts is directed at it; some electrons strike a phosphorescent screen; the electron microscopists select the field and the magnification which show the features they wish to demonstrate; the image may be enhanced; photographs are taken; some are selected as evidence. One can immediately see how far the tissue has travelled from life to an illustration in a book.

I sought permission to do some of the control experiments, and was told that they would be a waste of time, 'controversial' and I would not be able to get the results published. Neither the Science Research Council, the Medical Research Council, nor the University of Surrey would support such a project. So I wrote a book about the uncertainty of biochemical techniques.[29] Well known publishers turned down my manuscript. The University of Surrey Press published it as its first book and printed 2,500 copies. It sold out in Britain and the United States, but the publishers would not allow me to write a second edition. In 1975, unknown to me, the Russians translated it and sold out 12,500 copies.

The book was reviewed by *Nature*, the *Times Higher Education Supplement*, *Science Progress* and *Acta Biologica Academica Scientia Hungarica*. In the latter, Dr. Sandor Kerpel-Fronius wrote, "I feel strongly that the uncertainty is far from being as absolute as Dr. Hillman postulates. It should be remembered, for example, that in situ experiments with radioactive tracers and those carried out in vitro on isolated organelles or enzymes are very often in essential harmony in spite of the unquestionable shortcomings of the methods used. Such corroborative results should assure us that the present understanding of at least

some biochemical processes is close to reality."

At the time, I regarded this as the substantive answer to my reservations about biochemical techniques. While each technique only gave an approximation to the whole picture, the whole story put together produced a consistent picture.

The most hostile reviewer of my book was Professor J. Lucy of the Royal Free Medical School. He wrote, in *Biochemical Education*,[30] that I had overstated my case "in stating that the validity of a localisation of an enzyme activity is dependant upon all fifteen assumptions listed being warranted," then he added "(sic)." This implied clearly that he himself did not believe that the conclusion of an experiment *must* depend upon all its assumptions being warranted — he was saying this to lecturers, teachers and students. He pointed out a real mistake I had made about liquid scintillation although it did not affect my argument.

Light microscopy and the brain, University of Surrey, 1965 to date

Mr. Peter Sartory, although an amateur, was in my judgement one of the most expert British light microscopists. He was a distinguished natural historian, a former microscope manufacturer, an amateur astronomer, a former Committee Member of the Royal Microscopical Society, and former President of the Quekett Microscopical Club, founded in 1865. By the time I met him in 1967, he was chronically ill with lung disease, having smoked heavily all his life.

I had recently returned from Sweden, and asked Mr. Sartory if he was interested in looking at single fresh mammalian nerve cells dissected out from the brain by the technique which Hydén had used to examine the properties of cells.[31] Hydén himself had agreed that it would be useful to look at these cells by a variety of light microscopical techniques in the unfixed state, which is the nearest to the living state in which cells can be examined.

Hydén always took the cells out in a sugar solution,[32] but we tried taking them out in saline, which was more natural. Immediately, we saw a membrane around the nucleolus,[33] which had not been seen before. We tried to publish this finding, even resorting to the very ancient practice of sending the editor of various journals not only the photographs, but slides of cells showing our membranes. We demonstrated it to the distinguished microscopist, Dr. John Baker, who agreed that he could see it. The journals turned it down, firstly, because it had not been shown by electron microscopy, which distorted it[34]; secondly, it had not been seen before; thirdly, we had not shown that our membrane consisted of lipids and proteins, as the Davson-Danielli and the Singer-Nicolson models assumed. We pointed out that any lipids in the original membrane would not have survived the extraction by alcohol and propylene oxide during preparation for electron microscopy — despite all textbooks of life sciences showing cell membranes they believe to be of this composition. So far, there has been a Trappist response to this rather awkward point by the many electron microscopists with whom we have tried to discuss it.

I have never understood the reasons for resistance to the belief in the nucleolar membrane, even although we have published many photographs of it[35] and offered to send microscope slides to anyone in the world who wanted to see it.

Electron microscopy

Although at that time we did entertain doubts about the value of electron microscopy in biology of tissues containing much water, both of us still felt that the best source of information about the fine structure of cells was probably electron micrographs. We were comparing our high contrast light micrographs of unstained nerve cell bodies with the latest electron micrographs. We suddenly noticed that the endoplasmic reticulum, which is a network believed to be a structure in the cytoplasm (the cell sap), appeared to be cut

perpendicular to the section far too often than solid geometry would permit. It was as if one threw into the air a large number of coins, and when one photographed them, the vast majority were to appear edge on — instead of in all possible orientations. Unfortunately, this was also true of all the apparent membranes in the cell, the Golgi apparatus, the mitochondrial membranes, the cell membrane and the nuclear membrane.

Whereas we did not doubt the existence of the cell, nuclear and mitochondrial membranes, their sandwich ('trilaminar') appearance was simply impossible in solid geometry (Fig. 1). Obviously, if they were random, they should be seen as flat sheets as often as they are seen in almost perfect transverse section. After we had begun to doubt the existence of the cytoplasmic network (the endoplasmic reticulum) and the Golgi body on *geometrical* grounds, we suddenly realised that if they existed, they would not permit the intracellular movements which are generally regarded as evidence of the life of the cell. These movements can be seen by low power light microscopy, while there is supposed to be a fine network throughout the cytoplasm requiring very much higher magnification to see. Furthermore, iron filings, carbon particles or pollen injected into the cytoplasm spread quite freely, quite unimpeded by any fine network which would shackle them.

Thus we had two quite different lines of evidence — each of them powerful enough to question the existence of all the new structures in the cytoplasm seen with the electron microscope, plus the Golgi apparatus. When we were satisfied that we had overwhelming evidence, we submitted a paper for publication. The Editor of *Nature* rejected it on the grounds that the referee believed that no one at that time (1975) still believed in the 'unit membrane' or that the reticulum was attached to the cell membrane or nuclear membrane, but added that he agreed with us. *Science* gave no reason for rejection. *Scientific American* would not consider it as it had not been previously published; after it had, they still would not accept a small piece about our views. Nor would *La Recherche* or *New Scientist*. The latter wrote to me that it did not accept controversial articles, in a letter I received the same week as it featured Dr. Rupert Sheldrake on the exceedingly controversial concept of 'morphic resonance.'

As for the assertion that no one then believed in the 'unit membrane' or that it was attached to the cell or nuclear membrane, I listed all the latest books on life sciences in the reference collection of the University of Surrey; every single one of them indicated that they believed the former points. At meetings of learned societies, whenever anyone alleged that these beliefs were no longer agreed, I produced photocopies of these lists, and challenged those who had denied my assertion to name one textbook or paper (other than our own) which said that it did *not* believe in the 'unit membrane' or the attachment of the reticulum to the cell and nuclear membrane. Subsequently, the cytologists replied, "You don't want to believe what you read in textbooks." We were so horrified by this latter sentiment that we wrote a letter to *Nature* asking anyone at the Physiological Society, the Anatomical Society or the Royal Microscopical Society to justify this view in writing.[36] No one replied. So we put this list in a book we subsequently wrote on cell structure.[37]

Let us be clear what was happening. Firstly, senior research workers recommended only textbooks containing description of cell structures with which they disagreed; then they denied that these structures were so described; then they could not name any books or papers describing what they taught as the correct cell structure; then they alleged that one should not believe what one read in textbooks; then they were not prepared to justify such cynicism in print. The situation has not changed.

Most cell biologists today believe that intracytoplasmic movements of subcellular organelles occur, but also that there is a fine dense cytoskeleton in the cytoplasm; they

believe that the image of the cell seen by electron microscopy is three-dimensional, but have to tilt the stage to show some of the orientations. Thus, the views they hold about cell structure are inconsistent. This is extremely worrying, because the use of so many approximate techniques in biochemistry is usually justified by the assertion that together they make a fully consistent story. If they do not, the justification for using such popular techniques becomes even weaker, and the urgency to examine the validity of the procedures even greater.

We were quite unable to obtain publication of our paper showing that all the structures in the cell first shown by electron microscopy *plus* the Golgi body were artifacts. Among the criticism we faced was that we were not electron microscopists, although I had been using the instrument for 17 years when this was first said. Even if it were true, we believe that we do have a right to use the currency which authoritative electron microscopists have put into circulation.

Another tactic used against us was to label our ideas as 'old hat.' Critics said that ideas had been considered in the 1940s and 1950s, when the electron microscope was first used for biological tissues, and refuted then. Unfortunately, they could produce no references to support this assertion. Another trick was to say that all biochemists and cytologists studied artifacts. This was a smart way of avoiding discussions of which artifacts gave useful information about cells and which did not. A social trick was to exaggerate or joke about our views. Said one chairman, "As you know, Dr. Hillman does not believe in membranes — ha-ha!." At a coffee queue at a Physiological Society Meeting at University College, London, I heard two students agreeing that "Hillman's views are rubbish." "Have you ever read any of his papers?" I asked. "Of course not, I would not waste my time."

Among the more difficult questions raised by our critics were 'What do you mean by truth?,' 'What is an artifact?,' 'When is it useful?,' 'What do you see when you look down a light microscope?,' 'What is the nature of the image seen by the electron microscope?' It is only fair to say that these questions are not usually raised when one submits a paper on the structure of cells for publication. Various well-meaning, but perhaps naive, friends suggested that if we expanded our manuscript into a book, also dealing with these fundamental questions, we might have a greater chance of publishing it.

With the Audio Visual Aids Unit of the University of Surrey, we made a 35-minute film, and I showed it at the International Physiological Society Meeting in Paris, the Biochemical Society in Cambridge, the Society of Experimental Biology at Brighton, the Quekett Microscopical Club in London, the Physiological Society at University College, London, and other places.

At University College, Dr. A. Lieberman, the well-known electron microscopist, said after the film had been shown that he had many pictures of the endoplasmic reticulum and the 'unit membranes' in all orientations, which we had denied. Since his laboratory was close at hand, I suggested that he go to get them immediately to show the audience. His laboratory was untidy, he said, so I asked him if he would show me these micrographs if I called on him. I telephoned him five times altogether, but he would not send me any micrographs or references showing the images I requested. He did, however, send me an interesting reference on interpreting electron micrographs, which I did not feel was a relevant response. I offered to announce it in public, if I were to receive a micrograph showing a full range in the expected incidence of any of the structures whose existence we had doubted, but the full range would have to be in the *same picture*. That offer still remains open.

In 1977 I was invited to give a 40-minute paper at the 1979 Leopoldina Symposium on 'Cell Structure' in Thuringia, Germany, but when I arrived, I found that I was not on the programme. The Secretariat would not accept

my paper for publication on the grounds that it had not been received beforehand, although I had sent in the manuscript over six months before. I offered the Secretary another copy, but was told that it was too late. As I was waiting, I heard the Secretary telling a young research worker, who apologised for bringing her manuscript with her, that there was "plenty of time." When I pointed this out, the Secretary became confused, and referred me to the organisers. Nevertheless, by dint of diplomacy, I showed my 35-minute film, and it was followed by a 50-minute discussion. My paper was not included in the proceedings.

We had written a paper which we could not get published, a book that solicitous referees were sure would be published by another publisher, and a film which was irritating audiences. One day, I was invited to show our film by the Bristol Fine Structures Group, which was composed mainly of electron microscopists. Professor Richard Gregory, the psychologist, was in the audience, and asked me if we had ever tried to get our views published. Yes, I said, but without success. Had we thought of *Perception*, the journal of which he was editor? I said that our geometrical points were suitable for his journal, but not the biological ones. He asked me if I would be prepared to rewrite the paper to emphasise the geometrical arguments. Mr. Sartory and I were rather reluctant to do this, and then have the paper rejected for publication. Eventually we agreed to rewrite it and submit it, on condition that we did not have to leave out any points of substance. It was eventually published,[38] and the editor told me that "I have had a lot of stick from the electron microscopists for doing so."

About July 1977, Mr. Sartory suggested that we had to open a 'second front' — that was, we had to tell the *public* about this situation. I was reluctant, and it took him three months to persuade me that we had properly explored all the usual scientific channels. He telephoned the London *Observer*, and I was interviewed by its then science correspondent, Mr. Nigel Hawkes. He kept trying to discuss the economic consequences of the enormous cost of electron microscopy in medical research, and I kept trying to talk about the scientific points. About three months later, a short article appeared on the front page.[39] Exactly a week later, the *Observer* published a letter from the senior elected officers of the Royal Microscopical Society.[40] They said that our views had been generally rejected "in the light of overwhelming evidence to the contrary." They said that biologists had not seen our views in print. (We thought that this was somewhat cynical, since some of the signatories of the letter had resisted the publication of our manuscript).

Two weeks later, we replied.[41] "We know of no circumstances in which our views have been generally rejected… Nor do we believe that in scientific discussions, the correctness of an idea is measured by the number of its supporters." We ended, "The protagonists of the current view have so far been remarkably reticent in discussing with us these important questions. May we, Sir, through the hospitality of your columns invite the distinguished signatories of the letter, or anyone else who agrees with them, to debate these questions in front of a scientific audience at any place or at any time."

Two years later, although I had lectured widely, no one had responded to our invitation, so we repeated it in the *Observer*.[42] One debate eventually occurred, Dr. John Douglas of Brunel University arranged it with Dr. A. Robards of York University and the Royal Microscopical Society and Dr. K. Roberts of the John Innes Institute on the one hand, and Mr. Peter Sartory and myself on the other. By that time, Mr. Sartory was so ill that he only spoke for a few minutes. Dr. Robards started by saying that he was speaking in a private capacity, not representing any organisation. The new point he made in reply to the question about why most of the membranes appeared edge on in electron micrographs was that, like a barn door, one would not necessarily see it if it were open. I replied by asking why one did not see a *space* corresponding to

the size of the door when it was closed. Mr. Anthony Tucker, the science correspondent of the *Guardian*, gave a short summary of the meeting,[43] and Dr. P. Evennett, a signatory of the letter attacking us,[44] wrote an account in the *Proceedings of the Royal Microscopical Society*.[45]

We wrote to Sir Peter Medawar, the Nobel Prize Laureate who has published several books of advice on 'good' science, telling him that we would like to see him, and enclosing a four-page summary of our views; we pointed out that these would be understandable to a student aged 15. He replied that he could not comment as he was not an electron microscopist, but he referred our letter to 'his' electron microscopist. Five polite letters and ten years later, we have not heard from 'his' man. A recently knighted Oxford professor invited me to discuss the matters; I travelled all the way from Guildford (taking about four hours each way), but he only had 20 minutes to see me, not enough time, I suppose, to comment on what I said or offer me a cup of coffee. He passed me to his electron microscopist, who, after 15 minutes, said, "I have to go to lunch."

A famous textbook writer agreed that the Robertson model of the 'unit membrane'[46] was impossible, but said that he could not take it out of the next edition. When I asked him why not, he smiled benignly. At about that time, the publisher Mr. Michael Packard agreed to publish our book,[47] in the belief, which we shared, that biologists in general would be very interested in a new look at the structure of the living cell.

As I travelled round, there was hardly a single place at which I lectured where several people did not come up to me when I had finished and say that they agreed with us. I always asked them their names. Would they be prepared to say in public that, for example, they did not think the cell membrane was trilaminar (Fig. 1) or that there was a reticulum in the cytoplasm? (Mentioning our names was not necessary.) One lecturer in Edinburgh, whose name I did not note, said he would. All the others had reasons why they could not: they were writing theses, seeking lectureships, applying for grants, or being considered for chairs. Did I blame them? Do you? What would happen to their careers if they embraced controversial views?

In 1981, not long afterwards, BBC Television made a 'Horizon' programme, 'No one will listen to me.' It took the cases of Professor John Laithwaite, Dr. John Hastead and ours. A fair attempt was made to summarise our views, but these were 'answered' anonymously by the programme — those disagreeing with us not appearing. Of course, this gave the impression that our views were so ridiculous that the 'Establishment' did not itself want to counter them. Needless to say, we had answered the particular points several times. Although the producers of the programme did not intend this, the effect was most unfair to us. Nevertheless, the programme no doubt gave our views more visibility than desired by our critics.

Soon after the broadcast, I was taken off all undergraduate teaching in the University of Surrey, without any reason being given. I was an elected member of the Senate. So I asked at a meeting attended by the Dean and the Heads of the Biological Departments whether I had been removed from the teaching because of my views on cytology. I pointed out that I was the senior physiologist, that I taught relatively little cytology, and that I told my students the accepted wisdom because I wanted them to pass their examinations. There was no answer. The Department of Human Biology was closed down a couple of years later. Although I was the second senior person in the department and had London University degrees in medicine, in physiology and in biochemistry, I was the only member of that department not placed elsewhere in the University.

Our policy in the 1970s had been to refuse to speak to school or undergraduate students, because doubts at that stage might discourage them from learning biology at all. However, we changed our minds, firstly because we realised that ten to sixteen year-olds were

being taught about the reality of structures we said were artifacts at a time when they believed that everything they learnt was gospel truth. They were so conditioned. Secondly, we were persuaded that motivated young people often learned better when they were presented with opposing views. Thirdly, even the briefest acquaintance with the history of science teaches us that advances have nearly always been made when established views were re-examined.

Mr. A. Bishop, the Editor of *School Science Review*, which was widely read by school science teachers, invited us to submit a manuscript. We wrote an 11-page paper.[48] Two groups of electron microscopists, Dr. R. W. Horne and Dr. J. R. Harris,[49] and then Dr. R. H. Michell, Dr. J. B. Finean and Dr. A. Coleman[50] took issue with us in writing; they acknowledged the help of Professor W. E. Coslett, Dr. A. W. Robards, Dr. J. Burgess, Dr. S. Hunt and Professor H. W. Woolhouse. They attacked us, inter alia, for not having dealt with the considerable volume of data from biochemistry which they believed supported their view. Although we had cited it several times in our paper, they had failed to notice that our views had originated from a book I had written about just this subject.[51] We wanted to reply to the points made by the electron microscopists. Our original paper had been 12 pages long, and theirs together added up to 25 pages, but we were only accorded a letter of five pages to reply. We therefore decided to list the 11 questions which we had raised[52] which had not been answered. We wrote to all the authors of the two papers and those whom they had acknowledged, inviting them to an informal discussion of the differences between us. Only Dr. Michell replied, and he was not willing to discuss these matters with us. He was subsequently elected a Fellow of the Royal Society.

This brings up some fundamental questions about the behaviour of scientists. Do they have a duty to engage in serious dialogue about their published work? Is it satisfactory that they should not answer letters? What should students think about this? I subsequently published a full-length paper addressing all the points our electron microscopic colleagues had ever raised in discussion with us or in publication.[53]

Structure of the brain

Every day pathologists examine beautifully stained thin sections of brain. They see the nerve cells and occasional nuclei clearly but most of the section does not stain at all, when viewed by light microscopy. In 1846, the great German histologist Virchow gave the name 'neuroglia' or 'nerve glue' to this unstained material.[54] The general consensus among neurobiologists today is that there are four kinds of cells in the brain and spinal cord, besides the blood vessels. The nerve cells are the excitable cells, which show up; the nuclei belong to the other cells, the neuroglial cells, classified into astrocytes, oligodendrocytes and microglia. The neuroglial material is believed to consist of the three latter types of cells, with very little space in between them.

After I had been taking out nerve cells for about 17 years, by Hydén's technique,[55] I conceived of the idea that Virchow was right — the unstained material in the brain was *not* composed of neuroglial *cells*.[56] I did a series of experiments lasting another five years, and they all supported the following conclusions. There are relatively few, widely spaced nerve cells in the brain and spinal cord. Any cell with processes (like wires) is a nerve cell. The greatest proportion of the central nervous system is a ground substance consisting of a fine granular material with 'naked nuclei.' I published this conclusion in a monograph[57] containing much evidence from the literature as well as my own experiments. It contained blurred micrographs, was camera-ready, and was expensive. Dr. J. R. Parker reviewed it in a neutral fashion in the *Lancet* and Professor Brian Leonard was laudatory in *Neurochemistry International*, but it sold badly.

I was also unwise enough to find that the evidence for the existence of the synapses — by which nerve cells are believed to

communicate — contains so many inconsistencies, that they are likely to be staining artifacts.[58] I analysed transmission, whereby signals are believed to pass from one part of the nervous system to another, and concluded that the view that transmission was chemical, formulated in detail by Professor Sir Bernard Katz,[59] contained too many unproved and unprovable assumptions for the theory as a whole to be acceptable.[60] I have also spoken about this at many meetings, but so far no one has addressed my objections to the theory. However, I felt a duty to propose an alternative hypothesis.[61] Of course, there is not enough room here to give evidence for these conclusions, but they are given in detail in the *published* references cited.

Closure of the Unity Laboratory

In 1988, the Vice-Chancellor of the University of Surrey forced me to take 'voluntary' early retirement, on the following grounds.

- The University was short of money. (It has since acquired enough to set up five research professorships, and has received £30,000,000 from its Research Park.)
- The University had selected those areas which it wanted to support, but mine was not among them. (I have never been able to persuade the University to tell me (1) what committee met, (2) whom else it considered to select my work for not supporting, (3) why I was not asked to submit my publications or an annual report of my laboratory's work, or (4) why my laboratory's work was *not* submitted to the University Grant's Committee for evaluation.)
- My work was of poor quality. (I had published at least 80 full length papers, mostly in refereed journals, and I had written three books by 1988.)
- I had not obtained outside funds. (Nor had about 70% of the academic staff.)

The Senate on 30 September 1987 approved a 'Revised Academic Plan' for 1987-1990,[62] in which all departments were cut by 5%, but my laboratory was to be cut by 100%, that is, closed. This was approved by the Council of the University on 18 December 1987.

I took drastic action. On 5 November, I presented a paper to the Finance and General Purposes Committee showing that my laboratory was the cheapest in the faculty, that most academic staff members of the University of Surrey did not have outside funds, and that I had an above average research output. At least 12 of my senior friends, mostly from abroad, wrote to the Vice-Chancellor supporting me, although he did not report this to Senate or Council. Articles about the proposed closure appeared in the *Times*, the *Guardian* and the *Times Higher Education Supplement*. Two resolutions opposing the closure of the Unity Laboratory were passed unanimously at the Annual Council of the Association of University Teachers in 1988. A question was asked in Parliament.

The Handicapped Children's Aid Committee of London, which founded the Unity Laboratory and financed it from 1968-1981, rallied around and promised me support for one year. Dr. David Horrobin, Managing Director of Scotia Pharmaceuticals, who had himself suffered for his scientific views in Canada, also came to my aid. With this outside funding, the University agreed to allow my laboratory to remain open for a further three years, but without any support from University funds for my research.

'Voluntary' retirement

Not long afterwards, I was asked to take 'voluntary' early retirement. The University offered to buy in seven years of my pension, to give me a lump sum, and to reengage me for 40% part time. The total financial settlement would leave me with almost as much income as if I were still a full-time assistant professor, but I would lose my tenure. I was given three two-day ultimata delivered by the hand of an Assistant Secretary of the University.

The Association of University Teachers took legal advice in my support. Our University had one of the strongest tenures in the country. I had thought that I was fully

protected. However, the Association advised me that if the University dismissed me illegally, I would have to take legal action against it. If I won, damages to me would only relate to my loss of income, *not* my senior position, research facilities, prestige, etc. Such a case had not been heard before. The certainty of my winning was not by any means absolute. The consequences of failure of my plea would be financially disastrous to me, and I had a wife and four young children to support. The Association advised me to take the offer.

Reluctantly, I agreed to surrender my tenure under a number of conditions, not all of which were met. I believe that I am the only tenured academic in Britain who has lost his tenure because of his or her scientific views. Strangely enough, a few months before, I had ended an article on academic freedom in the *Times Higher Education Supplement* with the sentence, "Would you not be thankful that you had tenure, and lived in a democratic country?"

I have continued my full time research work with my colleague Mr. David Jarman in the Unity Laboratory. We have produced an atlas of the human nervous system,[63] and I have written a book, originally entitled *Letter to Students of Biology of the Twenty First Century*, now with a new name.[64] I have also listed the mechanisms whereby the dissemination of unpopular views is prevented in liberal societies.[65]

In recent years, without any reason being given, I have been prevented from presenting my views at a joint meeting in Würzburg of the German and British Physiological Societies (they told me that mine was the only paper they would not allow to be presented). The European Society of Neurochemistry would not allow me to speak at Leipzig. The British Society of Neuropathology prevented me showing a film because the Society said that it had seen it before — remarkable, because it had never been shown before. The joint meeting of the Norwegian and British Biochemical Societies at Eidsvoll invited me to send in an abstract and then would not publish it; they said that it was only because the film could not be understood unless one saw it, *but* they would not tell me how many others had been refused publication. At a meeting in August 1992 of the European Society of Neurochemistry in Dublin, although I was a founder member, I was speaking on a subject relevant to most other papers, and had requested an oral presentation, I was given the last slot at 5.15 pm, after 171 papers at the end of a five-day meeting. The chairperson did not turn up, the room was changed, several speakers did not arrive, and several others who wanted to hear my talk missed it. I received an apology, but no redress.

Present situation

I have shown, to my own satisfaction that (i) at least some popular important biochemical research techniques have never been controlled, (ii) most of the new structures in cells apparent by electron microscopy are artifacts, (iii) there are only nerve cells and naked nuclei in a ground substance in the brain and spinal cord, (iv) there are no synapses, (v) the transmitter hypothesis is doubtful. I have published all the evidence for these statements, although this has not always been easy.

The stakes are high. If I am right a very large proportion of experiments in basic research in life sciences will have to be completed, and this may result in quite different conclusions. If I am wrong, only my reputation is destroyed. It would be natural for a lay person to think that it would be very unlikely that any single individual was right and nearly all other life scientists wrong. Even if my conclusions were totally correct, it is very unlikely that they would be acted upon, because there are so many academics, doctors, teachers and publishers who have a vested interest in current views. History tells us that this does not happen quickly.

Every day that goes by more people have carried out more experiments apparently compatible with the current consensus, therefore more people have a career interest in

it being correct. At the same time, in Britain at least — where academic tenure has been virtually abolished — it is unlikely that anyone who raised the fundamental questions or came to the same conclusions publicly as Mr. Sartory and I have, would ever be appointed to a lectureship, be awarded a large grant for research, or enjoy a successful career in science.

There is a widespread belief that medical and biological research is very successful[66] and, therefore, more resources should be put into it. I have differentiated between two aspects of medical research. Since the 1940s, many new drugs have been discovered and developed empirically, intensive care units for dying patients have been set up in most large towns, new antibiotics have been found empirically and modified, transplantation of skin, kidneys and other organs has become routine, cardiac surgery has become a major speciality, and steroids have been used for skin diseases. All these have been highly successful applications of simple *technologies*. However, we must ask what has been discovered about the *genesis* of cancer, multiple sclerosis, Alzheimer's disease or schizophrenia. The answer is remarkably little which has helped us to understand the *mechanism* of the diseases, so that we can design rational treatments for them. The same may be said about the understanding of the molecular mechanisms by which drugs act; a large amount is known about *what* they do, but remarkably little about how they act in the living person or animal.

If we leave aside my hypothesis that basic medical, biological and pharmacological research has not been successful because it has not addressed the fundamental problems and assumptions inherent in most of the techniques, the current situation is dangerous because it suppresses free thought, without which the advance of knowledge can only be slow.

Message for the future

Irrespective of the truth or otherwise of my views in biology, I believe that it would be generally agreed that there is an international tendency to increases in: size of research units; complexity of research; cost of carrying it out; competition for academic positions; power of those who decide on the allocation of research funds; influence of those who control prestigious research journals; and censorship by the establishments of access to the popular media. It would also be agreed that knowledge can only advance when the current consensus is challenged. This is usually a consequence of thought by one or a few individuals, who by definition constitute a minority. Thus it is reasonable to be concerned that current trends will increase conformity and decrease individual or minority challenges, which will slow down the advance of knowledge.[67]

In addition, the large number of mechanisms discouraging the dissemination of challenging and new ideas will discourage intellectual honesty,[68] which is the overwhelming force which advances knowledge. Thus, the present situation will discourage academics from free thought. I would like to give a historical warning to all biologists that, unless they address some of the fundamental questions which I have raised[69] they are in danger of spending the whole of their research careers, using thermodynamically illegal procedures, studying artifacts, repeating uncontrolled experiments, indulging in intellectual casuistry or becoming cynical — none of which is good for science.

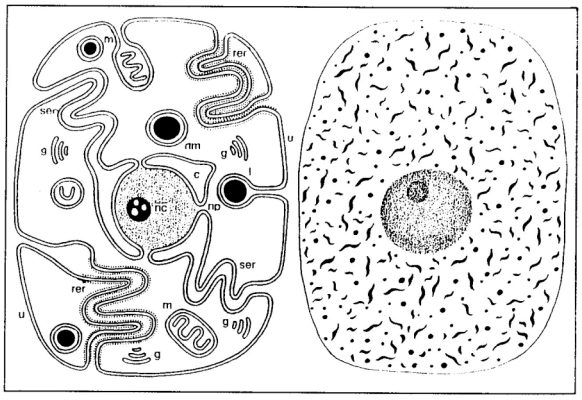

Figure 1. The structure of the cell, at the left as agreed by most modern cytologists and at the right as believed by me. In the structure on the left, *u* is adjacent to the double cell membrane, *g* to the Golgi apparatus, and *ser* and *rer* to the endoplasmic reticulum, a network in the cytoplasm. *m* is a mitochondrion containing the 'shelves' of cristae. *np* represents holes in the nucleus, the 'nuclear pores.' In my publications, I have shown that the double cell membrane should not always appear to be cut at right angles, and the reticulum or network would prevent intracellular movements which are characteristic of living cells. In the structure on the right, the mitochondria appear in the cytoplasm smaller and are oriented randomly. Further details are given in references.[70]

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