the uniqueness of my psyche or soul to a supernatural spiritual creation. To give the explanation in theological terms: each soul is a new divine creation which God attaches to the growing foetus at some time between conception and birth. It is the certainty of my inner core of unique individuality that necessitates the 'divine creation'. I submit that no other explanation is tenable, neither the genetic uniqueness whith its fantastically impossible lottery nor the environmental differentiations which do not *determine* one's uniqueness, but merely modify it.

An appealing analogy is to regard the body and brain as a superb computer built by genetic coding that has been created by the wonderful process of biological evolution. On the analogy, the soul or psyche is the programmer of the computer. Each of us as a programmer is born with our computer in its initial embryonic state. We develop it throughout life. It is our life-long intimate companion in all transactions. It receives from and gives to the world, which includes other selves. The great mysteries are in our creations as programmers or experiencing selves and in our association throughout life with our computers, as is diagrammed in figure 2, across the frontier.

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The regulation of order in cell communities

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The recognition of the difference between self and non-self is an essential feature of life within any system – whether the system be a single cell, a multicellular organism, a coral reef, or the largest ecosystem of which we have any knowledge, the biosphere of this planet. Every living creature is marked, in one fashion or another, as its own self, different from all other creatures of the same species and widly different from all other species. In effect, the life of the earth is made up of unique individuals. Uniqueness, if associated with mechanisms for the recognition of signals indicating individuality, makes a certain kind of biological sense. If you are going to set up a living system, with the implication contained in the term 'system' that the various members must relate to each other one way or another, as collabora-

tors and partners or as predators and prey, you would need to install unambiguous markers in order for the players to engage in the game.

For almost all of the known mechanisms of selfmarking, the labels are coded for by the organism's DNA, and the only truly identical creatures are clones arising from a single parent cell. Even this is not, however, a universal rule. Koshland's laboratory[8] has provided evidence that the individual, genetically identical, motile bacteria arising within a clone are genuine individuals, quite different from each other in their behavior. When they are tethered to a glass slide by their flagella, each bacterium can be observed to tumble and rotate in its own peculiar way, and the specific motile behavior is consistent and characteristic for each organism throughout its lifetime.

The individuality of more complex cells, including all of the eukaryotes, is determined by the molecular configurations of chemical markers at the cell surface. The need to preserve individuality, and to resist intrusion by cell populations with different surface markers, is among the most ancient aspects of nature. Examples can be found among the earliest metazoans, in animals which appeared in evolution long before the emergence of the vertebrate immunologic apparatus. For example, Jacques Theodor[9] found that two fronds of soft coral, of the same species but from different parts of the reef, will at first fuse together to become a single frond when placed in apposition but later on, after a few days, a zone of necrosis develops along the line of juncture and they will separate from each other. If one explant is much larger than the other, the small one will get the signal and will destroy itself by the lytic action of its own enzymes and vanish, bow out so to speak. The phenomenon involves the recognition of specific non-self signals, and resembles graft rejection in higher animals. Hildeman[4] has recently reported a similar rejection phenomenon in sponges. When two sponges of the same species, but from different colonies, are fixed closely together, fusion is followed by rejection in 10–12 days. Then, when the sponge explants are turned so that different surfaces of each confront each other, rejection occurs within 3–4 days. This accelerated rejection appears to involve specific memory contained within each population of sponge cells, a property mediated in vertebrates by lymphocytes. There are no cells resembling lymphocytes in sponges, but maybe the motile amoeboid cells in these animals possess the capacity for molecular memory, remote ancestors perhaps of lymphocytes. Hildeman's work has not yet been confirmed, so far as I know, but I hope others will pick up this extraordinary, important problem.

Single cells can recognize each other as though they wore name tags. When a mixture of free-floating cells from different organs – retinal cells and liver cells, say – are rotated together, they tend to rearrange themselves in clusters made up of identical cells, even forming tubular structures in the process of reaggregating.

During the morphogenesis of an embryo, surface signals of some sort, perhaps glycoproteins, provide the guidance mechanisms which govern the programmed sorting out of fetal cells, forming one specialized organ after another.

It is a curious anomaly that with all the evidences of cellular individuality and the tendency of individual cells to home together, the strange phenomenon of cell fusion exists, seeming to violate all rules of self-preservation. Under the right circumstances, you can persuade two cells from totally different species – even a plant cell and an animal cell – to fuse together and become a single cell with two nuclei, and then the two nuclei fuse into one, and then, mirabile dictu, the hybrid cell possessing two totally different genomes divides and produces generation after generation of its combined selves. Some of the chromosomes may be ejected along the way, and the use of man-mouse hybrids has turned out to be a powerful tool for the mapping of various biochemical functions as the human chromosomes are jettisoned.

There is something obviously unnatural, almost by definition, about cell fusion involving cells from different species. Since it usually requires the presence of an agent which alters the surfaces of the cells involved – Sendai virus, for example, or polyethylene glycol – it may be a purely laboratory artefact without any counterpart in nature. But something rather like fusion, involving the insertion of DNA from one cell species into the genome of an entirely different species, does occur in nature as a perfectly natural process. The most spectacular example that I've heard of is the arrangement between a bacterial species and its plant host which results in the cancer known as crown gall[7]. Here, the bacteria pass along a segment of their DNA into the infected plant cells, which then begin coding out a set of nutrients for the bacteria themselves, the opines. This is an example of recombinant DNA at work long before the Asilomar conference began worrying about this technology. The transformed plant cells gain the advantage of immortality from the arrangement, although from the point of view of the whole plant this is of course hardly an advantage; its singular advantage, it seems to me, is for oncologists.

Something like this, but more beneficial all around, may have happened in the emergence of the symbiotic partnership between the rhizobial bacterial and the root cells of bean plants, on which all the rest of us depend for the fixation of nitrogen from the earth's atmosphere. The bacteria and plant cells become so closely associated as to form a single tissue, and it has been proposed that the production of leghemoglobin

by the plant cells (which is essential for protecting the nitrogenase enzyme system) may have come originally from genes inserted by the bacteria[2]. Like the partnership between mitochondria and eukaryotes, and between chloroplasts and plant cells, this is one of the earth's great successes in symbiosis, handy for us all.

Some types of free-living cells exhibit self-awareness at an intracellular level, and, at the same time, the capacity to recognize non-self entities when these appear within the cell. *Amoeba proteus* has been found to be particularly good at this, thanks to the work of Jeon[6] and his associates and the devising of a neat technology for transplanting the clean nucleus of one amoeba into the cytoplasm of another. Jeon's story begins with the spontaneous infection of his amoeba cultures by rod-shaped bacteria, since designated as X-bacteria. At first all the amoebae were made ill by the encounter, and many of them died off. Some, however, struggled along despite the infection, and gradually became acclimated to the situation, carrying along their parasitic bacteria from one enfeebled generation to the next. After several months, the health of the amoebae had returned to normal, but now they had become dependent on the bacteria and were unable to live without them. When the bacteria were eliminated by raising the temperature of the amoeba cultures from 20 to 26.5 °C, the amoebae themselves died off.

More recently, Lorch and Jeon[6] have found that the process of adapting amoebae to a state of dependence on their bacterial lodgers involves a permanent and irreversible genetic change in the amoeba, and this transformation takes place within as short a time as 4 weeks, involving no more than 10–15 generations of amoebae. The changed genome was revealed by transferring the nucleus of an X-infected, adapted amoeba into the cytoplasm of a normal, uninfected amoeba of the same strain. When this was done, the cell receiving the nuclear transplant died within a few min. Oddly enough, when the nuclear transplantation was made in the other direction, from a normal amoeba to an infection-dependent cell, the new nucleus was tolerated without any evidence of damage. It is well established that an amoeba nucleus can be transplanted into the cytoplasm of any other amoeba of the same strain, but heterotransplants – between amoebae of different strains – are lethal. Thus, it is fair to conclude that the process of adaptation to the X-bacteria had sufficiently altered the amoeba nucleus so as to produce the effect of a foreign strain. The fact that the lethal action of nuclear transplantation only worked in one direction suggests the possibility that the adapted nuclei now possess an *added* component, making the nucleus, in effect, a foreign self-plus-X entity. Such a cell might not recognize anything foreign in a transplant of a normal, non-X nucleus, in the same sense that female tissues can be successfully grafted to a syngeneic male mouse but not the other way round; due to the added, and foreign, influence of the Y chromosome.

It is, of course, possible that the adapted amoebae are altered because of an insertion of bacterial DNA into its genome, as in the crown gall model, but the details of the molecular genetics of this extremely attractive model are not yet in.

There are some free-living single cells that look and behave as though they were whole multicellular organisms crammed within a single cell membrane, and perhaps they were in fact pieced together at an earlier period in evolution by the joining up of two or more separate types of cell. This sort of partnership must have been formed long ago for all the eukaryotes when the bacterial ancestors of mitochrondria joined up, and when blue green algae became the chloroplasts of plant cells. The protozoan *Myxotricha paradoxa,* which lives in the intestinal tract of an Australian termite and carries the full responsibility of digesting the termite's diet of wood, is composed of at least 3 different creatures; the protozoan itself, a dense layer of spirochaetes permanently attached to its surface which beat in absolute synchrony to provide motility, and a great number of oval bacteria embedded in its flesh which are believed to be the source of the digestive enzymes. None of the 3 components can live without the other two. It is not really an organism, it is more like a committee.

The strangest creature of this chimaeric, dream-like variety that I have read about is Blepharisma[3], a ciliated sporotrich that lives in ponds all around the earth. This protozoan has as elaborate and differentiated a morphology as many metazoans – a mouth fringed on one side by an undulating membrane and on the other by a layer of cilia resembling an eyelash; hence the name Blepharisma. There are several distinct nuclei, sometimes as many as 20, one of which, the macronucleus, is responsible for the details of morphogenesis while the others are involved in reproduction. There are granules containing a photosensitive pigment, a hyperricin, all around the inner side of the membrane – so photosensitive in fact that if the creature swims into direct sunlight, as it does from time to time, it is immediately killed. Blepharisma looks like a committee that had been put together by another committee. The world is not a perfect place. From time to time nature, like Homer, nods.

The best of all experimental systems for studying the expression of selfness and individuality is the mixed community of lymphocytes and macrophages in inbred mice. Here the facts are literally pouring in, filling more journals each month than used to be devoted to the entire combined fields of experimental medicine, physiology and pathology with the latest news of T-cells, B-cells, monocytes, basophils, eosinophils and the complex interactions among all these

and other types of tissue cells. It has become an immensely complicated problem, but one central feature dominates all others and governs and modulates all interactions among the cells: the function of any particular cell, and its functional relation to the others in the community, depends on the specific molecular signals it displays at its surface.

Moreover, the study of immune cells is beginning to provide the best of all models for exploring developmental biology, with analogies at every hand for processes that are fundamental to the commitment and deploying of the cells of a developing embryo.

And, moreover still, a close look at these cells may reveal something on a tiny scale that marks all the life of this kind of planet: the interdependency of living things and the setting up of essential partnerships, the phenomenon of symbiosis which is essential for the survival of living systems. All by iseelf, a B-lymphocyte would seem to be fully capacitated for the manufacture of its own special idiotype of antibody, fully in charge of its own destiny, ready to respond to the particular antigen to which it is committed. But, as it turns out, it cannot make a move without the presence in its immediate vicinity of a thymus-derived lymphocyte, a so-called helper cell. A solitary T-cell, ready to respond to viruses, foreign cells, parasites of various sorts and also cancer cells, cannot do so unless the antigen is processed by a macrophage and then presented in association with an entirely different antigen, the self-marking MHC antigen displayed by the macrophage itself, coded for by the major histocompatibility complex genes of the host. The action of helper cells is balanced and modulated by the countervailing action of T-suppressor cells. It is a network, operating by feedback, checks and balances.

There is a strong possibility, amounting almost to a certainty, that some of the major diseases of human beings occur when things go wrong with the balanced interaction of cells of the immune system. Autoimmune reactions are not pathologic in themselves; indeed the existence of accurate sensors for the identification and precise location of self-markers is as important for the operation of the system as is the capacity to locate non-self antigens. But when the autoimmune recognition mechanisms is unconstrained, as may happen when microbial agents enter the blood or tissues equipped with cross-reacting antigens which mimic the surface molecules signalling self, or when viruses lead to the immune destruction of all the cells which they occupy, or when something happens to impair the action or accuracy of T-suppressor cells, one or another disease state ensues. The possibilities range all the way from rheumatoid arthritis and lupus to multiple sclerosis to the lesions of tertiary syphilis and tuberculosis to cancer to, conceivably, the decay of the whole organism caused by small molecular errors in the process of aging.

But when it is working at its normal best, this same system is responsible for the surgically precise elimination of foreign cells, viruses, bacteria, parasites of all sorts, and perhaps, the still-disputed but still conceivable immunosurveillance mechanism which provides 75% of us with lifetime protection against the successful emergence of clusters of cancer cells[10]. In mice, the system is under the genetic governance of the H-2 locus of genes, in man, HLA. By this system, one's own cell surfaces are consistently recognized as one's own unique self, distinguishable from those of all other selves.

There is still another system at work to the same end, but apparently a fundamentally different one[12]. We possess unique odors, each one specifically and uniquely our own.

A well-trained tracking hound can follow the footsteps of any human being across a field, and distinguish with accuracy that particular track from the path of any number of other human beings crisscrossing the same field. The evidence for this is largely anecdotal, but the literature of anecdotes has been abundant and consistent for a great many years; in addition, there is a sizable archive of well-controlled experiments, most of them carried out in Europe in the 1920's and performed by hard-boiled pragmatic members of the police departments of various countries. As far back as 1875, the geneticist Galton made the prediction that a tracking hound should be unable to distinguish between the tracks of identical twins, and a series of experiments by Kalmus et al.[5] in the 1960's tends to confirm the prediction, although not yet conclusively. The point is a crucially important one, and the experiments need redoing with an abundance of controls for household smells, diet, soap, shoes and so forth. If it could be shown once and for all that uniovular twins leave tracks that are identical, but different at the same time from all others, we would know, once and for all, that each of us is marked by his or her person-specific genetically-determined odorant.

If true, it should not come as a surprise. Indeed, it would be a strange thing, and something of a surprise, if it were not so. Self-marking by odorants is a commonplace circumstance elsewhere in nature. Minnows and catfish have been shown to be able to smell the difference between each other as individuals, and mice, as we shall see, have the same gift. These days, when as Edward Boyse has remarked, the proper study of man is mouse, we are permitted a certain degree of extrapolation from such observations.

I became interested in this matter several years ago, when invited to deliver an address before an Immunology Congress on possible future lines of immunologic research. It occurred to me then that it would be remarkably unparsimonious of nature to set up two such elaborate and complex systems for individual

self-marking, costly in terms of energy, one involving the immunologic markers of histocompatibility and the other using olfaction, and have these two mechanisms evolving without being closely related to each other. I made at that time what I thought was a mild biological joke, predicting that the same set of genes would be found responsible for both systems of labelling, and that someday 'man's best friend would be used for sniffing out histocompatible donors'[11].

A while ago I was discussing this with Dr Edward Boyse, whose research laboratory makes daily use of an extensive collection of meticulously inbred and sharply defined lines of mice. His wife, Jeanette Boyse, had the immediate responsibility for overseeing the breeding of various lines of congenic mice, in which the sole genetic differences between 2 lines lay in the H-2 locus on chromosome 17, the locus governing graft rejection and coding out the major histocompatibility complex (the MHC) of tissue antigens. The mice were contained in transparent boxes so that their mating behavior could be kept under close and constant observation. Mrs Boyse had just noticed that the males of certain lines displayed a preference for mating with females of the opposite line possessing the different H-2 genes. The possibility was raised that perhaps the male could smell the difference, and since these were 2 lines of genetically identical animals, except for the H-2 difference, it was obvious that the capacity of a male to smell such a difference would have to involve an olfactory distinction between self (in strict terms of individual self) and non-self.

It did not take long for the Boyses, together with two young postdoctoral fellows at Sloan-Kettering, Drs Yamazaki and Yamaguchi, to establish with satisfactory statistical significance that the phenomenon of mating preference between H-2 congenic mice was real and consistent[14]. We then moved on to a simpler system for getting at the same problem, which involved, at the outset, training a tracking mouse.

In brief, the technique was based on the classical Y-maze, with 2 different odors coming down the arms of the Y, one from the tracking mouse's own line, the other from the congenic line differing from himself only at the H-2 locus. The reward for selecting the correct arm was a drop of water, and the tracker was urged to seek the drop by being deprived of water for the preceding 24 h. Training was begun by teaching the mouse to distinguish between the odor of cinnamon and juniper; then, when he had got the idea, he was trained to discriminate between the smell of his own and a totally different breed of mouse, and finally to detect the odor of the congenic line, in this case the difference between B-6, his own line, and B-6 H-2^k, the other strain.

The experiments worked, and have continued to work, with a surprising degree of consistency and reproducibility. A group of smart tracking mice have been taught to smell H-2 during the past 3 years. Each experimental trial involves 24 runs toward the target, which is changed from one arm to the other at random, and the correct or incorrect choices are recorded by a third party who is himself unaware of the correctness of the choice. With a very high degree of statistical significance, each tracker has learned to distinguish between his own smell and the congenic smell when the odor box leading to the arm of the Y-maze contains mice of the proper genetic line. The odor is not detectable in homogenates of various mouse tissues, including spleen, liver, kidney, lung or brain, nor can it be detected when mouse embryos are in the box. However, it is readily detected, with an accuracy even greater than when whole live mice are in the odor box, in samples of urine[1,13,15]. The tracker can detect the odor of congenic urine when the urine is contained in a petri dish in the odor box, and the smell is still perceived when the urine has been diluted 1:40. The odorant is surprisingly stable, withstanding boiling for 1 h. It is a small enough molecule to pass through a dialysis sac.

We have learned that the same odorant can be detected in the urine of F-2 segregants derived from crosses between the 2 congenic lines, effectively ruling out smells derived from parental environment or family litter boxes.

The same odor is responsible for the phenomenon of pregnancy-blocking, the so-called Bruce effect. This is the peculiar reaction which occurs when a newly impregnated female is placed in contract with a strange male: the pregnancy is promptly terminated and the female goes into estrus. She does not do so, of course, when the contact is with the original stud responsible for her pregnancy.

Using 2 congenic lines of mice, differing only at H-2, Yamazaki and the group have found that replacing the original stud with a different male of the same line does not cause the Bruce effect, but when the new male is of the line with a different H-2 locus the pregnancy stops and estrus resumes in the majority of females. The actual presence of the H-2 foreign male is not needed for this effect; the same results occur when the pregnant female is in the immediate vicinity of a sample of urine from the appropriate line.

The Bruce effect is not induced by exposure to females of the congenic line, nor by urine from such females. Thus the Bruce effect must be caused by the perception by the pregnant female of 2 distinct and separate signals, one indicating maleness, the other announcing the presence of a male with a different H-2 locus.

I know of no satisfactory explanation for the Bruce effect, not anyway in teleological terms. Perhaps it represents a built-in response which tends to enhance heterozygosity and, to some extent, to impair close

imbreeding. Or perhaps - and this is the teleology I prefer - the mere presence nearby of a strange male, differing in the odor of his H-2 from the original stud, signifies the departure of the father and the loss of protection to be expected from him for the forthcoming litter, and therefore it is time for the female to give it up and start over again. Our experiments have told us nothing about this, only that the smell of male strangeness is coded by the same string of genes that code for immunological strangeness.

Last year, Dr Boyse and I had the opportunity of observing tracking dogs at work, first at the dog-training station of the Baltimore police department, then later at the Scotland Yard station just south of London. We saw enough to convince us that the specific and selective tracking of a man was a genuine and reproducible phenomenon, and that it ought to be entirely feasible to set up experiments to settle the question of whether identical twins leave identical tracks and even - although here I can envisage only some formidably difficult technicalities - trying to correlate tracking accuracy with human HLA types. Needless to say we have not set out on either of these lines, but some of the things we have already observed are perhaps of anecdotal interest even if not scientific value. One curious thing I had not known: when a hound sets off on the track of a designated man, he does so not with his nose close to the ground, as in the movies, but rather tossing his head high, from side to side, as he goes. When the track turns at a sharp angle he overruns it, of course, but when he comes back to regain it he does so by sniffing the air well above the ground's surface, getting clues not from the ground itself, or from footprints, but from something rising away from the ground.

In the Scotland Yard trials, we brought along several squares of gauze that had been placed in the bedding of various cages containing the two congenic groups of mice, B-6 and B-6 H-2^k, and asked the trainer to see if his dog could learn to distinguish between the two. The squares were laid out at random, at intervals over a long slab of glass, the dog was given the scent of the one to be selected, and he trotted rapidly along with his head held several inches above the gauze squares until he reached the correct one, which he picked up neatly in his teeth and brought back to his master as though carrying the evening paper. The whole operation seemed so effortless as to be nearly automatic, and from the dog's point of vew, the easiest of things. If we humans possess pheromones that label each of us as a person, I am glad to say that we cannot, as a rule anyway, smell them, social life being complicated enough as it is, but it would not surprise me at all if a Scotland Yard hound could do so, and could readily pick up the fragrance of any one urine sample and tell it from all the rest.

But even within the technical imitations of the tracking mouse and the Y-maze, it ought to become possible to learn something now about the chemical nature of the H-2 coded olfactant in mouse urine. Indeed, Drs Yamazaki and Yamaguchi have recently transferred their laboratories to the Monell Institute in Philadelphia, where the chemistry of odorants is a high-technology speciality, for this purpose. There will surely be some interesting questions. What sort of heat-stable substance can it be, possessing enough variability in its structure as to provide unique self-markers for all the numberless individual mice, or, for that matter, all 4 billion human beings? I would imagine that it will turn out to be a *set* of chemicals, probably of the same class but with structural variations, a cis-arm here, a trans-arm there, arranged in infinite numbers of possible medleys, possibly very small changes in the intensity of one or another member of the group, and with each individual's odor sounding as a unique chord.

Perhaps some similar arrangement of groups of molecular signals will account for the apparently infinite variability of cell-markers in the immunologic system. It is conceivable that MHC is a similar set of different signals, displayed in varying concentrations to achieve uniqueness. It is not beyond imagining, I should think, that the actual molecular configurations which fire off the olfactory receptor cells might turn out to be the same, or closely related to, the ones that, in the end, fire off a T-lymphocyte. And, to carry the matter as far as it can be stretched, it is even imaginable that some signal arrangement of this sort is at work in the homing of embryonic cells, the self-preservation of sponges, and the preservation of internal privacy within an amoeba. If so, it adds something more to the complexity of life for the single cell. It is not a simple life to be a single cell, although I have no right to say so, having been a single cell so long ago myself that I have no memory at all of that stage of my life.

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If for Walter Rudolf Hess order is the essential principle of all life, a similar principle of order can be traced in the personal biography of this great scientist and physician. Born 1881 in Frauenfeld, he spent his childhood in this city of eastern Switzerland, where – to use his own words – the whole surrounding was in full harmony with his psychic constitution. Already at the age of five he used to explore the fields and meadows, to collect plants, and every new specimen meant an exciting experience, for it was brought home and carefully classified with his father's help. The latter, professor of physics at the 'Gymnasium', gave him the opportunity to enjoy an early contact with classical physics which would be of great importance in his later life. During the years at the 'Gymnasium' his father allowed him to visit his laboratory and to help him in setting up the experiments for his classes. Already at this time Hess relized that the seemingly stationary processes in the so-called static systems were, in reality, a system of antagonistic forces resulting in dynamic equilibrium. During the last semesters at the 'Gymnasium' he decided to take up the medical profession which seemed to him the ideal way to apply sciences for the benefit of people. His first choice was the University of Lausanne, then Bern, the capital of Switzerland, then Zurich, Berlin and finally Kiel. Already during the first semesters at the university he published at the suggestion of W. Roux, the anatomist from the University of Halle, a paper entitled 'A mechanically induced conformity in the structure of the vascular system', a most fascinating contribution dealing with the relationship between hemodynamics and the morphological formation in the arterial system. In 1905, Hess received his degree in medicine at the University of Zurich. The choice of the place for his first internship was dictated by financial circumstances, which did not allow him to follow a study in theoretical medicine as he would have liked so much. He therefore took a post as resident in the state hospital of his home Canton with the department of surgery under the direction of Dr C. Brunner. There he soon became interested in the relationship between the morphological organization of the vascular system and the flow characteristics of blood factors determining circulatory phenomena. Hess constructed a convenient apparatus to measure blood viscosity for clinical use, the so-called *Viscosimeter.* Based on measurements with this original instrument were the results and conclusions published 1906 in a small treatise entitled 'Viscosity of the blood and the work of the heart'. The essence of this paper is the demonstration that the viscosity of the blood varies with the number of circulating erythrocytes. A further suggestion is that decreased viscosity of the blood can lead to turbulance. This basic and important paper was later accepted as his thesis by the medical faculty of Zurich.

After this first year of internship, Hess wanted to work in some branch of medicine which would give him sufficient time to devote himself to problems of basic research. A practice in ophthalmology seemed ideal in order to meet these requirements. He therefore seized early in 1906 the first opportunity to enter the department of ophthalmology at the University of Zurich as a resident working under Prof. O. Haab, an outstanding clinician and skilled ophthalmic surgeon. Although the mainly morphological orientation of research work in this department did not quite correspond to Hess' interests, he had ample opportunities to make diagnostic observations of more functional and dynamic character. Already in the first years at the University Eye Clinic of Zurich, he became engaged in the *problems of analyzing oculomotor disturbances.* In contrast to the old complicated techniques