I was happy when Mrs. Gimbel and Dr. Rinkel invited me to come to participate in this meeting, and I have been happy to attend the symposium on the chemical basis of mental disease, and to be associated with the Manfred Sakal Foundation, because of its dedication to the job of diminishing the amount of human suffering in the world.

Recently, the world has been changing at a tremendous rate. Technological advances are such that the world is not the same one year as it was the year before. Tremendous weapons of destruction are developed. The stresses under which people live become ever more oppressing. There emanates from the centers of governments a special sort of irrationality. Among the people there are rejections of dogma and revelation, the old principles of conduct. We are forced to strive for a fundamental, ethical, and philosophical principle under which we can live, if the world is going to survive.

I think that the fundamental ethical principle that everyone can accept is that of the minimization of human suffering. This is not the same as maximizing the amount of happiness in the world. If we take money as the criterion, to increase the income of, say, a billion people by a hundred dollars a year is not at all equivalent in the amount of happiness that it causes to decreasing the income of the other two billion by half of that amount. It is the amount of suffering, human suffering, that we have to pay attention to.

As the means of communication and transportation, telephones, telegraphs, the press have developed in the world, the nature of the human race has changed. No longer are individual human beings the units. They are now bound together by these means of communication in the same way that the cells of an individual human body are bound together by the nerves that interconnect them, in such a way that the whole human race is becoming one organism, and a special ethical

principle will have to be developed under these circumstances. But it must not be an ethical principle that places the survival of society or the race above the value, the worth of the individual human being. ~~It is the individual human being and his suffering to whom we must pay attention.~~

~~Now~~ there are many causes of human suffering. In some parts of the world starvation, malnutrition, infectious diseases are the principal causes; but everywhere mental disease is an important cause, and ~~more~~ in the U.S. half of the hospital beds in the country are occupied by mental patients. Mental disease causes a particularly great amount of suffering for two reasons: First, it may continue in an individual year after year, ~~it fluctuates in~~ causing him great suffering for and his friends and relatives. And second, often it attacks some of the most able of our people, ~~also along intellectual lines.~~ It may well be that schizophrenia is an especially significant disease for the most able intellectuals. This is a disease that we must attack. We must cut down on the amount of suffering caused by mental illness.

I am grateful to the psychiatrists. For several years, ~~half a dozen years,~~ I have had close contact with them, ~~not, as some people have suggested it, because I needed professional service, but~~ because I became interested ~~some years ago~~ in the question of how chemistry might contribute to medicine, might be used in diminishing the amount of human suffering, and I decided that mental disease was the field in which there was the greatest need of effort.

~~I am still~~ I am grateful to the psychiatrists, even though they do a rather poor job because they don't know how to do any better. They use crude methods, insulin shock, electro-shock therapy, damaging the whole human organism in the hope that the new changed individual will be in some way improved.

The psychiatrists now use drugs, ataractic drugs, that are valuable, that have been obtained not through any process of radial summation, not because of any understanding of the ~~causes, because there is a complete lack of understanding of the~~ nature of the diseases; but because by purely empirical processes, it has been found that for some patients, these drugs are helpful, valuable. These drugs were not discovered rationination, based on the they were discovered empirically, when they were to be helpful

I hope that the psychiatrists will not have to work much longer under this terrible handicap of extreme ignorance, and I am encouraged by the information that what is presented at this symposium, information about most interesting and valuable leads about abnormalities in the biochemistry of schizophrenia individuals, or other people who are suffering from mental disease, as compared with other human beings.

I am encouraged to believe that the time will come before long, in ten or twenty years, when, if enough attention is paid to this job, there effort is made, will be some significant fundamental, basic understanding of the nature of the group, I think a group of diseases that we classify as schizophrenia, and other mental diseases, comparable to that which exists now for a few other diseases that are called molecular diseases.

I believe that most mental diseases are molecular diseases, the result of a biochemical abnormality in the human body. Of course, I think that the psyche, that consciousness, the mind, is a manifestation of the structure of the brain, an electrical oscillation in the brain supported by the material structure of the brain, and that the mind can be capable of being altered by an abnormality made abnormal by an abnormality in the material chemical structure of the brain itself, usually xxxxxxxxxxxxxxxxxxxxxxxxxxxx or hereditary in character, but sometimes caused by an abnormality in the environment.

Pellagra is an example of a disease with mental manifestations that was prevalent years ago. It is a deficiency disease, due to a lack of vitamin, nicotinic acid. This discovery has led to the solution of the pellagra problem in many parts of the world.

In the field of mental deficiency, there is some understanding about molecular mental disease. For example, the disease phenylketonuria, first identified 30 years ago by Dr. Foelling in Oslo, Norway, who checked up on some mentally deficient children who had an odd smell and found that there were some unusual substances present in their urine; further investigation by him and other scientists led to the discovery that these children lack an enzyme in the liver that catalyzes the oxidation of an amino acid, phenylalanine, to tyrosine, so that the phenylalanine builds up in the bloodstream and cerebrospinal fluid to high concentrations, interferes with the development of and function of the brain, and leads to mental deficiency.

Foelling

~~One person in 80~~ ~~In the United States, every person~~ carries ~~a~~ one gene for phenylketonuria. Normal people have two genes that manufacture the enzyme in the ~~liver~~ liver that catalyzes the oxidation of ~~phenylalanine~~ phenylalanine to ~~tyrosine~~ tyrosine.

~~You know,~~ the proteins that we eat, ~~such as in the meat and the fish and potatoes and bread, the proteins that we eat~~ contain about 20 different amino acids: glycine, alanine, serine, tyrosine, ~~melalinicine~~ phenylalanine and so on. We eat more than we need of ~~it~~ and not quite enough tyrosine. There is an enzyme in the liver that catalyzes the oxidation of ~~febraticine~~ phenylalanine to ~~terracyine~~ tyrosine.

Most people have two genes, ~~that~~ which they have inherited from their parents, that manufacture the enzymes in the liver to do this job. One person in 80 has one gene that manufactures the enzyme, and one damaged, mutated ~~abnormal~~ gene that ~~won't~~ does not manufacture the enzyme. ~~won't do its job or else there is an abnormal enzyme molecule that will not do its job.~~ Accordingly they have only half the amount of the enzyme that a normal person has. ~~But that's~~ This is, however, enough to keep them in good health.

in the blood and other body fluids and interferes with the growth and functioning of the brain,

But if two of these people marry one another, there occurs the great lottery: the child inherits only one of the two genes from the father and one of the two from the mother. A quarter of the children thus inherit an abnormal gene of the father and an abnormal gene of the mother, and which neither will manufacture the enzyme. There is none of the enzyme in the liver. As the child eats its food the phenylalanine builds up, causing him to be mentally deficient and to have severe eczema and other manifestations of the disease.

But when this knowledge was obtained, it was found that the disease could be recognized a few weeks after birth. Then the child can be fed a diet of hydrolyzed protein from which the phenylalanine had been removed. He will then develop in a nearly normal manner.

But nevertheless this disease, which in the past has been responsible for 1 per cent of the institutionalized mentally deficient individuals in the United States, now may be brought under control because of the discovery about its nature.

Let me talk about another disease that I know more about. It is not one that leads to mental deficiency, but it is a molecular disease, with which I have a personal connection, because its molecular nature was discovered by three of my students working in Pasadena 13 years ago.

It is a disease of the blood, and a very important one. Perhaps 10 or 20 thousand people in the world die of it each year. Children are born with this disease; they suffer for a few years and then die;

~~tends to 20 years old, perhaps. This is caused, too, by such a disease.~~

This disease is a disease in which the ~~x~~ red cells of the blood are twisted out of shape. Often, instead of being flat, they are twisted into a sort of crescent shape that looked to Dr. J.D. Herrick in 1911 ~~something~~ like a ~~xxxx~~sickle with which one cuts grass. He named the disease sickle cell amenia. ~~It is easier to study the blood than the brain. It is easier to study hemoglobins than an enzyme in the liver, or an enzyme in the brain, say. The brain is going to be a tough nut to crack for people who are working on mental disease.~~

Hemoglobin makes up ~~1~~ 1 per cent of the weight of ~~an individual~~ a human being, ~~and you can get quite a bit out of anybody if you work in investigation.~~ It is a ~~very~~ beautiful protain, red, because the molecule, which contains about 10,000 atoms, has 4 ion atoms which are able to combine with oxygen in the lungs and carry the oxygen out to the extremities.

The red cells of these patients with Sickle cell anemia have these red cells which are twisted out of shape. They are only twisted out of place in the venous blood, not in the arterial blood. There they have the normal shape. As you see, there is the cleavage.

It is highly ~~possible~~ probable that it is the hemoglobin ~~x~~ molecule then that is responsible for the disease, because in arterial blood you don't have hemoglobin; you have instead oxygen; whereas in venous blood, there is something different. If these patients manufacture a sort of hemoglobin was different from that which normal individuals manufacture, these might be sticky molecules, self-complementary, such that they would clamp onto one another to form long rods which would line up side by side to form a long needle-like thing. It would be longer than the diameter of the red cell, and it would twist itself out of shape. They would be sticky and get tangled up with themselves and prevent the flow of blood through the capillaries and the various manifestations

of the disease would occur.

So, Dr. Tunneau and Dr. Singer, and Dr. Wells, after a while, with encouragement, carried out an experiment. They put a little drop of salt water, with electrodes at the ends -- a positive electrode and a negative electrode -- and introduced a drop of hemoglobin from a normal human being. In this colorless liquid, under the influence of the electric current, it moved over toward the positively-charged electrode. It had a negative electric charge.

When a drop of blood from a patient with the disease was put in the trough, it moved over to the negatively-charged; if it had a positive charge, it had to be different from the normal hemoglobin in the red cells of normal individuals.

If you mixed these two and put a drop of the mixture in the electric field, they separated; part of the blood moved this way; the rest that way. Then when they got blood from the father of the patient and the mother of the patient -- and Dr. Tunneau of our laboratory put a drop of hemoglobin from the father of the patient -- that blood split in half; half moved toward the anode, and half toward the cathode; and similarly for the mother.

This made the nature of the disease clear. The father and the mother had one normal gene that manufactured normal hemoglobin. Each had a normal gene, and each had an abnormal gene, and each of these genes manufactured its own kind of hemoglobin. Here we had an abnormal hemoglobin. And the patients had inherited only the abnormal gene of the father and only the abnormal gene of the mother.

Here was the demonstration, for the first time, of a disease of the hemoglobin molecule that produced the manifestations of the disease Sickle

cell anemia.

That isn't the whole of the story. A month or two later, Dr. Tunneau brought in some blood from another patient who had a still more abnormal hemoglobin, which was named Hemoglobin C, and then Hemoglobin D, Hemoglobin E, Hemoglobin G, Hemoglobin H, Hemoglobin I -- some 30 or 40 of these. I haven't kept track of them. Otu of these,abnormal hemoglobins have been found, many of them associated with the disease, even with diseases that result in sort of hybrid diseases that result from the inheritance of a Sickle cell amenia from one parent and the inheritance of a C gene from the other. Neither of these genes alone, in single dose, causes a disease that amounts to anytying, but the patient who has inherited both the first abnormality and the second abnormality in single dose has a disease, a new kind of hybrid disease, hemolytic anemia.

This example, I think, indicates what we can expect to find in schizophrenia, not that there is a gene for schizophrenia, such that when the patient inherits this gene in double dose he is schizophrenic, but rather that there are many genes such that any one of them, when present in double dose, or perhaps one single dose, and another one in single dose, or it may even be a combination of several of these genes, produces an abnormality, a quantitative abnormality to make it difficult for the individual to accept reality, to think in the normal state, or to retain his sanity under the normal stresses of living, or increasing stresses of living in the modern world..

There may be factors involved in schizophrenia that come from the outside deficiency factors, some lack of some vitamins, or perhaps toxic chemical substances that are present. Who knows?

The evidence that was presented to the symposium about the presence of some sort of a biochemical abnormality in the blood associated in some way with

the globulin fraction of the serum of the blood seem to me to be very suggestively convincing, because several groups of good investigators from different places using different methods of investigation had obtained somewhat similar results with the methods.

I feel this is a strong indication of an abnormality that is present also in the brain and that is involved in the disease -- in some of the diseases that we classify as schizophrenia. OF course, this multiple character of a disease will make it difficult to find a cure, a treatment. But for all kinds of schizophrenia, I can't say that I have any hope that mental disease can be brought completely under control. But I do believe that a tremendous amount of progress can be made in controlling it, and in decreasing the amount of human suffering that is involved.

There are ways for treating diseases that can be envisaged that have not yet been brought into practice and that are worth serious effort. For example, in an enzyme deficiency disease, galactocemia, or many of the other enzyme deficiency diseases. With the progress in our knowledge about the nature of enzymes, the structure of protein molecules, it will before long be possible to synthesize artificial enzymes that will have enzymic activity to perhaps implant a capsule containing some stable artificial enzyme as a substitution therapy that permits the patient to get along well in the course of his life, possibly with an occasional replacement.

New drugs will be discovered, some of them by the same ~~mpx~~ empirical process, by means of which the Aborigines discovered the ~~f~~ efficacy of chewing cinchona tobacco leaves in the treatment of malaria.

But the time will come when we shall have enough understanding of the nature of mental disease to be able to synthesize drugs to order that will be specific for a particular disease that will operate not in the rather generally nonspecific manner of the present drugs that are effective, that have changed

the character of mental hospitals greatly, but that nevertheless will still have to be described as representing a sort of shotgun attack on the problem of the solution of disease.

In the case of diseases, congenital diseases involving gene abnormalities, we have now to recognize the possibility of the DNA replacement -- replacement introduction into the defective individual of DNA molecules that will serve the purpose of the molecules that they did not inherit from their parents.

But, all of these are palliative measures. They are not the solution of the problem. The pool of human germ plasma, you know, continues to degenerate day after day, as the natural mutagenic agents, natural radioactivity, other mutagenic substances, and those chemicals and artificial high energy radiation that constitute a part of our modern life damage the DNA molecules constituting the pool of plasma. It is a very precious one.

A person can inherit about 100,000 molecules of DNA, 50,000 from his father, and 50,000 from his mother. If all of these inherited by every one of the 2 billion persons now living on earth were to be brought together -- could be brought together -- they would constitute a mass of about 4 milligrams, the size of 4 pinheads.

This is the pool of human germ plasma that I am concerned about. It becomes damaged -- damaged day after day by mutagenic agents, and it is purified. There is a natural process of purification that goes on. New genes for phenyluria are caused by this mutation process. The probability is something like one in a hundred births, or one in 50,000 children has a new gene for this. For example, there is a dominant gene that causes dwarfism. It is a dominant gene. The parents of a child who did not possess the abnormal genes, but had two normal genes instead, would between the conception of the parents and the conception of the child produce an abnormal gene that he inherited.

One child in 12,000 inherits this.

There is the disease cystic fibrosis. One child in 800 has inherited from its parents two genes for cystic fibrosis which give him this very serious disease -- and we don't know what these genes do. This is without doubt a molecular disease, but the protein molecule that is abnormal has not been identified.

Now when these defective children are born and die without progeny, they remove from the pool of human germ plasma 2 of the defective genes, and so there has been a steady state, such that some 4 per cent of the children who are born have some degree of mental defect; some 7 per cent are congenitally defective either physically or chemically.

I believe that it is possible for us now to begin to carry out the process of purifying the pool of human germ plasma at a rate to keep up with this continued contamination, without the suffering that is involved in the birth and death, without progeny of the defective children. If two parents have a phenylalanine, then it is known that they are carriers of the gene for phenylketonuria for each successive child; the chances are 25 per cent that the child, this child, too, will be defective. If two parents have a child with cystic fibrosis, or with many other diseases, Tasacks disease, nimintax disease, we developed a test, a rather difficult one, for detecting the heterozygous for phenylketonuria. One of the parents involved came to see us later. His wife had died. He knew that he and his first wife, if they had had further children, there would have been the 25 per cent chance. He came with a young woman that he wanted to marry, and he said he wanted to know whether she carried the gene for phenylketonuria. After the test was made, he was told she was not a carrier for phenylketonuria; that they could get married, and that none of their children would have the disease phenylketonuria;

of course they would have some other defects, because everyone inherits some congenital defects, mainly minor ones. The minor ones are not to be laughed at. They are a cause of a tremendous amount of human suffering, because they are not enough to prevent procreation, and the genes are passed on for generation after generation causing continuous adding to the amount of human suffering in the world.

But it is possible in many cases now to say that [illegible] offspring in this marriage would have a 25 per cent, each child being grossly defective. This is a great amount of human suffering, and I would say that it is too great a chance to be taken; that a chance as great as 25 per cent of giving birth to a defective child, increasing the amount of human suffering is so great that this matter should not be left to a combination of ignorance combined with free enterprise in life as is customary at the present time.

People need knowledge. People need to know what their situation is, and then of course to decide for themselves in these personal matters. I do not advocate legal action. I do not advocate eugenics as a means of improving the race. We don't know enough about how to improve the race; but we do know something about how to decrease the amount of human suffering, and if a heterozyal were to marry a normal individual as this man, the father did, then half of those children would inherit his gene. If the only thing that was done as a result of [illegible] increase in knowledge was to get people who possessed defective, seriously defective genes of a certain sort to marry other people who do not possess these genes, then there would be no elimination of the defective genes from the pool of human germ plasma, and pretty soon everyone would have a greater chance of being defective than he has at the present time.

I think that in the case of people who know that they are carrying a gene, a recessive gene for a serious disease, should marry normal individuals, and then have a somewhat smaller number of children than normal,

one or two children, rather than three or four. In this way these defective genes would be removed from the pool of human germ plasma slowly, perhaps at a rate that they are now being removed by the death and suffering of the defective children, but without the death and suffering of these children. This, I believe, is a humane and rational way of attacking the problem of disease, congenital disease caused by mutated genes, a way that does not involve the birth and suffering of defective children, and as the years go by, we shall be able to obtain for mental diseases, too, more and more knowledge about the diseases and methods of predicting whether one union has a high probability of leading to these defective births.

But, of course, we must also consider the question of palliative treatment. I wish that the support for investigators who are studying the biochemical abnormalities of schizophrenic individuals could be doubled, tripled, quadrupled. You know there are plenty of scientists, very able people in the world, who would like to be working on problems like this, but who are instead working on other problems the nature of which I haven't time to go into. But we have no need to have technological scientific unemployment resulting from disarmament. There is plenty of room for the scientist to do for the benefit of human beings in the United States and all over the world.

I believe that we are going to have a better and a better world in the future, and that the scientists are going to do their part in contributing to it -- and of course with the help of the psychiatrists, people who work in the field of mental disease. We couldn't get anywhere without the help of the psychiatrists.

I want to say again that as I have become acquainted with more and more psychiatrists-- and our eldest son is a psychiatrist now, 37 years old, and I think making a success in this profession, he seems to me to be a very good man, one of the soundest, most well-balanced men that I know. I think that

he is good for his patients; no doubt does the best that he can for his patients. I hope that my associates and I out in Pasadena will, as we continue with our work, which is on a small scale, carried out not with the hope that we can make any epoch-making discoveries, but with the firm confiction that we can do something that will be of aid to him in his future work, and to all of the fine medical men in the world who are devoting themselves to the treatment of the mentally ill.

Thank you.

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