Institute for Enzyme Research.

[Madison, Wisconsin]: [s.n.], [s.d.]

https://digital.library.wisc.edu/1711.dl/OXSQNXQ2GEV238Y

uw
news

From The University of Wisconsin News and Publications Service, Bascom Hall, Madison 53706 • Telephone: (608) 262-3571

Release: WEDNESDAY NOON, APRIL 29 4/28/70
Photos on request

UIR Science Writing Division (262-5984)

By LINDA WEIMER

MADISON, Wis.--(Advance for Wednesday noon, April 29)--The operation of a new energy form in biological systems has been discovered after a 20 year quest at the University of Wisconsin's Institute for Enzyme Research.

Drs. David E. Green and John H. Young, speaking at the annual meeting of the National Academy of Sciences Wednesday in Washington, D.C., revealed the mechanism by which energy is transformed in the cell's powerplants -- the mitochondria

"This is probably the key to energy transformation in all the cell's membrane systems, be it stomach secretion or nerve impulse transmission," said Green.

The problem of how energy is transformed in living membrane systems stumped researchers until the introduction of the electron microscope in the early 60s.

"With the high magnification," Green explained, "we saw the toadstool-like machines which fit together like bricks in a wall to make up the mitochondrion's membrane.

"When better methods for rapidly fixing mitochondria for study were developed, we could actually see these mitochondrial machines at work."

The researchers first found that these tiny machines undergo rhythmic pulsations, much like the opening and closing of an umbrella.

- more -

Subsequently, they observed that these structural changes always accompanied energy transformation.

"These pulsations," noted Young, also with Wisconsin's Theoretical Chemistry Institute, "led to our recent discovery that protein systems can become excited by oxidation just as simple molecules can be excited by light."

The energy stored in these excited machines is then used to perform work. In the case of the mitochondria, work constitutes either active transport or the manufacturing of ATP, an energy storing molecule.

Green and Young described to their colleagues in Washington how active transport -- the movement of chemicals through a living membrane -- can be explained by their model.

The Wisconsin team, composed of Green, Young, George Blondin, Martin Lee, Gary Vanderkooi, and David Allmann, are now directing their attention to the last key piece of the puzzle -- how the mitochondrial machine in the excited state can make ATP.

"We haven't yet devised a model to describe how this is done," Green said, "but we feel sure the pattern already established for active transport will point the way to the solution."

###

uw news

From The University of Wisconsin News and Publications Service, Bascom Hall, Madison 53706 • Telephone: (608) 262-3571

Release: **Immediately** 10/8/68

UIR Science Writing Division (262-5984)

By DENNIS MEREDITH

MADISON, Wis.--Nobelist Arthur Kornberg, the man who perhaps has come closer than any other to synthesizing life in a test tube, explained results of his latest research at a University of Wisconsin talk Monday.

Kornberg, winner of the 1959 Nobel Prize in Medicine and Physiology, told how he and his colleagues achieved the synthesis of workable DNA in a test tube. His visit to Wisconsin was sponsored by the University's Biochemistry Department and Institute for Enzyme Research.

DNA, short for deoxyribonucleic acid, is the template used to direct synthesis of all the major molecules controlling life.

Kornberg used DNA from a virus known as X-174 as a "guide" for his synthesis. By introducing the viral DNA into a solution of DNA building blocks, called nucleotides, and a coupling enzyme, called DNA polymerase, he was able to build a man-made copy of the DNA.

His DNA was able to infect bacterial cells just as the original viral DNA was able to. And even more important, the artificial DNA was able to produce more DNA--which was identical to the DNA originally removed from the living virus.

Kornberg's talk Monday centered on the mechanism of action of the enzyme which links together building blocks of DNA.

- more -

Modifying a popular phrase into more scientific language, Kornberg promised to "tell it like it might be." He said that the coupling enzyme had been found to be simple, though large. It was thought to synthesize the DNA chain by "holding" the template DNA and fastening the parts of the new DNA onto it.

Synthesis of the biologically active DNA, Kornberg explained, has opened tremendous possibilities for future research. By synthesizing DNA from tumor-causing viruses and altering it until the viruses are no longer dangerous, for instance, researchers might find ways of changing the virus when it actually infects a cell and thereby render it harmless.

For another example, if certain types of diabetes or other diseases were traceable to genetic deficiencies, artificial corrective DNA could be manufactured and given to a diabetic to correct the mistakes in his body's DNA.

This may be possible, biochemists explain, by using harmless viruses to "carry" pieces of DNA into the body cells to replace or repair the defective genes, or even to introduce new desirable traits.

Kornberg concluded: "This is truly the realm of genetic engineering. It is our collective responsibility to see that we exploit our great opportunities to improve the quality of human life."

###

uw news

From The University of Wisconsin News and Publications Service, Bascom Hall, Madison 53706 • Telephone: (608) 262-3571

Release: Immediately 12/14/66 mes

UIR Science Writing Division (262-5984)

By MARLETTE SWENSON

MADISON, Wis.--Solving the genetic code that determines the synthesis of proteins has been one of the most significant advances in genetics during the past year, an internationally-known geneticist believes.

"For several years, geneticists have suspected that the DNA codon, or coding unit, is composed of three bases," says Prof. James F. Crow of the University of Wisconsin. The codon, in other words, is a sequence of three chemical bases in an order which determines a certain amino acid in the protein.

"Geneticists now have overwhelming evidence for this belief," he writes in the recently published 1966 edition of Science Year, the World Book Science Annual. Written by recognized authorities in their fields, the volume communicates the recent achievements in science to the general reader.

Prof. Crow, chairman of the medical genetics department at Wisconsin and member of the elite National Academy of Sciences, is widely known for his research in population genetics.

"Under proper conditions, it is possible to synthesize proteins in the laboratory without living cells," Crow explains. If messenger-ribonucleic acid (RNA) is added to a mixture of amino acids together with the protein-assembling machinery from living cells, a protein is produced which corresponds to the code of the particular RNA, and therefore of the DNA in the gene that produced the RNA.

- more -

Investigators had been handicapped, however, because long RNA molecules with a known sequence of bases could not be synthesized.

"Finally," Crow writes, "H. Gobind Khorana and his associates at the University of Wisconsin were able to make long RNA molecules with a specific repeating triplet or a repeating doublet." This discovery, made at UW's Institute for Enzyme Research, was announced last spring.

"From the results of these and other experiments, the code is now practically solved," he says.

Elucidation of the genetic code--being able to "read" its message from the chains of chemical bases--has far-reaching implications.

For example, two of the codes, UAA and UAG, are particularly interesting. Instead of coding for a particular amino acid these codons stop the production of proteins at this point, Prof. Crow explains. "This suggests that these two codons may function as periods marking the end of a sentence. That is to say, they may signal the end of a protein in case a single messenger-RNA carries the message for more than one protein."

Occasionally some genes cause mistakes in protein synthesis, but, in some circumstances, such mistakes actually may be beneficial. "It sometimes happens that two wrongs make a right," says Crow, explaining that a mistranslation of the wrong code may correct the original error.

Finally, understanding the genetic code has made it possible to tackle one problem of evolution. Scientists know, for example, the approximate time required for the evolution of our present-day animals, including man, but they have little idea of how many gene changes were made in the process.

"It has been possible to measure the relationships of different species by the amount of difference in their proteins," Prof. Crow points out. "So far these measurements agree quite well with the relationships that evolutionists had deduced from other kinds of evidence--fossils and comparative anatomy."

###

NEWS FROM THE UNIVERSITY OF WISCONSIN
Statewide Communications Service, 10 Bascom Hall, Madison, 53706

10/13/67 jb

RELEASE Immediately

ENZYME ADDITION

MADISON--Final plans and specifications for an addition to the University of Wisconsin's Enzyme Institute in Madison were approved by the UW regents Friday.

The five-story addition is budgeted for $1,455,000, with state funds providing $805,000, federal funds the remainder. It will be located on University Ave., just west of the Naval ROTC armory.

The first four floors will hold offices, laboratories, storage areas, and rooms for equipment, special purposes, and instruments. The top floor, a penthouse facility for mechanical equipment, will be constructed over the present building and be linked with the new structure.

Construction is expected to start early next year and be completed in two years. The exterior will be tan brick, to match the existing unit.

###

U.W. NEWS

Research Enzymes

From The University of Wisconsin News and Publications Service, Bascom Hall, Madison 53706
Telephone (Area Code 608) 262-3571 Release: Monday, August 9
8/6/65 mes

By MARLETTE SWENSON

MADISON, Wis.--If it were not for the enzymes in our bodies we would not be able to live, for without them our bodily functions would proceed too slowly to sustain life.

Enzymes make life possible because they act as catalysts--that is, they speed up vital biochemical processes such as breaking down foods and releasing energy, but are not changed themselves by the reaction. With enzymes, our cells can do in one minute what would otherwise require several thousand years.

These complex organic substances are as vital to our bodies as the air we breathe or the blood flowing through our veins. Although as many as 700 varieties of enzymes are known to exist in the human body, scientists and medical researchers do not know yet the exact mechanism of their action.

"This problem is one of the important unanswered questions in biochemistry today," a University of Wisconsin researcher states.

Of the several theories proposed to explain enzyme action, the most widely-held theory says reactions at one site of the enzyme molecule are accelerated by functional groups elsewhere in the molecule. Chemists have tried for years to test this theory with model systems.

Now, new support for this theory has come from pharmaceutical chemists at the University of Wisconsin. Working with alkaloids, basic compounds from plants known as the veratrums, Prof. S. Morris Kupchan and his research group have discovered reactions which closely resemble the proposed activity of some enzymes.

-more-

Prof. Kupchan will describe these new findings at two scientific meetings in Europe in September. He will present one of two main lectures at a symposium in Bratislava, Czechoslovakia, co-sponsored by the Slovak Academy of Sciences and the German Academy of Sciences. Of chemists from 14 countries who will participate in the symposium, Prof. Kupchan will be the only representative from the United States. He will also explain his research at the Swiss Federal Institute of Technology in Zurich, Switzerland.

The recent developments grew out of extensive structural studies at Wisconsin on the veratrum alkaloids--extracts of plants such as Indian poke and white false hellebore.

Indian poke, also known as American false hellebore and, to the scientist, as Veratrum viride, is found in eastern North America. Its medicinal properties were known to the Indians for hundreds of years. Only during the past 100 years, however, have doctors known its powdered roots and rhizomes to cause a drop in blood pressure.

White false hellebore, with the scientific name Veratrum album, grows in Europe.

The active agents responsible for the potent blood pressure-lowering properties of the plants were isolated in pure form in the late 1930's and early 1940's. Chemists then began studying the structures of these agents in laboratories the world-over.

Structures of the active veratrum alkaloids were elucidated in the 1950's by Prof. Kupchan's research group. The results of their researches constitute the basis of over 50 scientific papers describing the complete structures of most of the blood pressure-lowering alkaloids isolated from these plants.

"During the course of our structural studies it became apparent that the hypotensive (blood pressure-lowering) alkaloids had very complex structures with many functional groups, or centers of chemical reactions," Prof. Kupchan explains.

Add two--Kupchan enzymes

"We noted several unusually fast reactions, and hypothesized that the fast reactions might be due to interactions between several functional groups," he says.

Once the structures were completely known, the researchers returned to a detailed examination of the accelerated reactions, and have recently discovered several novel effects involving catalysis of a reaction at one center in a compound by another functional group in the same compound. This phenomenon closely resembles the proposed activity of certain enzymes and lends support to the theory.

"Our observations strengthen the probability that such reactions may be involved in the action of some enzymes," he points out.

Prof. Kupchan was assisted in his research by Prof. Stuart Eriksen, Dr. Y. T. Liang, and graduate students John H. Block and Allen C. Isenberg. National Institutes of Health and the Wisconsin Alumni Research Foundation gave financial support.

##

Enzyme Institute

August 16, 1965

Prof. David Green
153 Enzyme Institute

Dear Prof. Green:

You will no doubt be interested in the story on pages 5-7 of this issue of the Oscar Mayer & Co. employee publication.

Thank you for your cooperation in obtaining this material for a local firm which has generously donated research material to the University.

Sincerely,

James F. Scotton, Director
News and Publications Service

JFS:ah
Enc.

U.W. NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON, WISCONSIN 53706

2/19/65

RELEASE: Immediately

By JAMES LARSEN

MADISON, Wis.--Energy is the key to life--lacking it no animal can hunt, no child can play, no eye can see, no brain can think.

A child knows he is alive because he can run. But carry the subject one step farther and it becomes the deepest of scientific mysteries. Muscles need energy to work--and the source of the energy is still unknown.

It is known, however, that intricate chemical machinery in the living cell is capable of extracting energy from the simple food substances carried in the blood and making it available for work.

Researchers at the University of Wisconsin Enzyme Institute in recent years have taken what appear to be very significant steps forward in understanding how the energy needed to sustain life is generated.

Here in laboratories on the Wisconsin campus the nature of the intricate chemical circuitry by which energy is shunted from cellular storage battery to working machinery is being outlined in some detail.

Muscular contraction is a good illustration of life's need for energy. But all cells, all tissues, all organs require energy--liver and kidneys, eyes and ears, heart and blood; even the brain expends energy for thinking.

In fact, in this latter case we have the interesting spectacle of scientists using gray matter to determine how the brain functions; how thought processes are energized.

Yet this is precisely what is being accomplished, with considerable success, and at an every accelerating pace.

-more-

Possibly the most medically useful discoveries will first come in improved knowledge of how muscles work. For the heart is just such a muscle, one with virtually incredible strength and endurance, yet one which ages and wears out, eventually losing its capacity for labor and losing its resilience.

It is of considerable significance that it is precisely the heart muscle that is used most extensively in this research on the secrets of the energy-source for living tissue--the secrets of the "spark of life."

In Wisconsin's Enzyme Institute, Prof. David E. Green, an enzyme chemist of world note, and his associates daily employ many pounds of the heart muscle of cattle--furnished for the research without charge by the Oscar Mayer Co. of Madison--as a source of the chemical machinery and for studies of the spark of life.

The program recently was given a $2.5 million supporting grant by the U. S. Public Health Service's National Institutes of Health, a grant which will permit Green's research group to probe more deeply into the chemical electro-generators of the living cell during the next seven years.

Their particular interest in beef heart is easily deduced. It is an unusually rich source of mitochondria--small, delicate, intricate cellular bits housing the chemical machinery generating cellular energy. In essence they constitute the assembly line for production of cellular storage batteries. The batteries--ATP molecules in chemical terminology--are charged in the mitochondria.

Viewed in outline, mitochondria are not especially complex. Powerfully magnified, a mitochondrion resembles a short sausage. Outside is a membrane enclosing the whole structure; inside are convolutions and folds which connect with the outer membrane.

Yet, a decade ago, even this much was not known about mitochondria. They were mysterious small dark particles floating among many equally mysterious objects in cellular protoplasm.

The work of the scientists in the UW Enzyme Institute, along with that of hundreds of other scientists throughout the world, including an electron microscopist at the University of Chicago named Humberto Fernandez-Moran, has given science a rather concise idea of the structure of the mitochondrion. Perhaps more important, these scientists have begun to clear up many questions of how it works.

The outer membrane is given over to one function; the inner folded membranes have another. The outer membrane extracts energy from a substance formed from blood sugar--the ultimate digestive product of energy-food substances. The energy is shunted into inner membranes where it is used to manufacture molecular storage batteries--the ATP molecules--and energy can then be obtained from these when needed.

The electron transfer system is made up of chemical units, each of which is a small particle given the name electron transport particle--or ETP for convenience. Countless numbers of these ETP bits are arrayed along the mitochondrial membranes like the cells in a honeycomb.

The Enzyme Institute scientists have shown also that the outer membranes house biochemical systems for the synthesis of fat, and that the energy for this synthesis is obtained from the ATP manufactured in the inner membranes.

The work of Wisconsin's Enzyme Institute scientists also has refuted a long-established notion regarding the initial breakdown of blood sugar in the first steps of the energy-extraction process. This initial breakdown of blood sugar--glycolysis--is now known to occur in the outer membrane of cells, not in the aqueous portions as formerly believed.

To accomplish extraction of mitochondrial enzyme systems, heart muscle cells are broken up in gentle grinders where continual low temperatures, just above freezing, are maintained. The proper chemical balance in the solution in which the cells are suspended prevents breakage of the weak chemical bonds linking ETP units to the membrane protein, and keeps the delicate systems intact.

Add three--enzyme institute

In the electron transport particle and the ATP-synthesis centers of the mitochondria lie the keys to the process by which living cells obtain energy. It also appears to account for the still somewhat more obscure processes by which atoms of such materials as calcium, magnesium, and other elements are passed through the membranes of living cells.

What developments in future medical progress will ultimately trace back to this research cannot now be foreseen--but it is virtually inevitable that the work will make possible many startling advances in the arts of healing. This will probably occur most specifically in prevention of many ailments most directly affecting such organs as the kidneys, heart, and circulatory system.

It is also giving science a more direct and detailed understanding of the chemistry of living things. The ETP units appear to be identical in all forms of life, from the smallest of visible organisms to the plants, the animals, and ultimately man himself.

It joins the other recent advances in biology--of which the discovery of the function of the genetic substance DNA is another--demonstrating that all life is based on an identical fundamental chemistry.

###

NEWS FROM THE UNIVERSITY OF WISCONSIN

Serving the state through campuses at Madison and Milwaukee, nine University Centers, and a statewide extension system.

10/12/64 db

Release: 10 a.m. October 13

By DENNIS BLAKESLEE

MADISON, Wis.--A day will come, perhaps not long from now, when any scientist can buy a genetic codebook for his laboratory.

The date of publication still awaits preparation of the full text, but it is approaching with breathtaking speed.

The newest in a lengthy succession of ever sharpening tools used by scientists to solve the code, the molecular instructions for life, was announced here Tuesday by a University of Wisconsin biochemist.

By combining known biological techniques of making artificial DNA, the molecule that carries hereditary information, with new chemical methods, Dr. H. Gobind Khorana and co-workers have produced long DNA molecules that are biologically active and have a known and repeating sequence of code letters.

In the DNA molecules of living organisms, various combinations of these small chemical code letters, which number only four in kind, compose up the genes that make a man differ from a horse, a tree differ from a rose.

Dr. Khorana, a co-director of the Institute for Enzyme Research at the University, spoke at the annual fall meeting of the National Academy of Sciences.

For several years, scientists have been able to make artificial DNA by placing a short piece of natural DNA into a chemical soup containing the raw materials for making more DNA along with a special chemical starter called an enzyme.

-more-

Using the short piece of DNA as a blueprint, or template, the enzyme exactly copies it over and over, running the copies together into a chain thousands of times the length of the blueprint.

The resulting long strand possesses all the properties of natural DNA, even to the point of being able, so long as the enzyme is present, to duplicate itself, the process by which hereditary information is passed from cell to cell, from parent to offspring.

Though the technique is highly valuable, the usefulness of the DNA produced is limited in that there is no way, as yet, of telling what the sequence of code letters was on the blueprint piece.

In the past few months, however, Dr. Khorana and his group have applied the enzyme, called DNA polymerase, to short chemically synthesized blueprints with a known sequences of code letters.

The resulting chain, the biochemist said, is still enormously longer but this time with the known sequence repeated again and again.

The chemical methods for making the known short pieces were perfected by Dr. Khorana and his colleagues last spring. The technique for making long chains by DNA with the enzyme was the work of Dr. Arthur Kornberg, now at Stanford University, for which he was awarded a Nobel Prize.

The availability of the new hand-tailored DNA holds exciting possibilities for biological and biochemical research, Dr. Khorana said.

In a special chemical system, the artificial DNA can be made to turn out bits of protein material. This, he pointed out, would supply clues as to what combinations of code letters spells out what proteins will be made by a cell.

In living organisms, each code sentence--a gene--directs the formation of a certain protein, the structural and functional chemicals of life.

The formation of the artifical chains also illustrates the incredible accuracy of the enzyme in copying the pieces of blueprint DNA, Dr. Khorana pointed out.

Though the blueprint chains might be but a dozen code letters long, the enzyme makes a chain many thousands of letters long, the same ones in the same order, over and over, without ever making a single mistake, he explained.

This accuracy is absolutely essential in living things, for if DNA were not faithfully copied every time it duplicates itself, which occurs whenever a cell divides, the delicate balance between life and non-life would be quickly and fatally upset.

##

U.W. NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON, WISCONSIN 53706

6/8/64 jl

RELEASE: Immediately

MADISON, Wis.--A Wisconsin Alumni Research Foundation grant of $1,808,552 to support research and allied scholarly work at the University of Wisconsin was accepted by the UW regents Monday.

It was the ninth annual WARF grant exceeding a million dollars and brought the total University grants from the foundation since its founding in 1925 to more than $23 million, exclusive of WARF funds given to the UW for campus laboratory construction.

The grant goes to the faculty research committee of the Graduate School for allocation to various projects conducted by investigators in all fields of study.

"WARF grants, over the years, have helped to make this University one of the world's great centers of research and scholarly work," Pres. Fred Harvey Harrington said. "While they cannot be used to replace any deficiency in the basic research appropriations from the State, they enable the University to move quickly into new, productive research directions and help build and hold a great faculty."

The major portion of the current grant, $1,353,935, has been allocated by the research committee to support various research and scholarly programs on application from individual faculty members.

Other allocations made by the committee include: $127,000 to support predoctoral fellowships, used to attract outstanding young scholars to the campus and perhaps later to the faculty; $60,000 for research appointments to assist in bringing potentially top new staff members to Wisconsin; $40,000 for postdoctoral fellowships; and $30,000 for symposia and lectures.

-more-

Add one--WARF grant

The committee also allocated $48,000 for special travel and for the Haight Fellowships, established in 1956 to finance travel by UW scientists to foreign laboratories for research and study, honoring the memory of the late Wisconsin alumnus and Chicago attorney, George I. Haight, one of the founders of WARF.

Other allocations are as follows: $25,444 for the Slichter Professorship; $29,833 for the Institute for Research in the Humanities; $26,000 for the Survey Research Laboratory; $15,000 for the University of Wisconsin Press. Funds allocated for amortization of three research buildings included $3,817 for chemistry, $20,600 for the Enzyme Institute, and $28,915 for chemical engineering.

The foundation was established 39 years ago on the initiative of Prof. Harry Steenbock to handle in the public interest his patent on the discovery that irradiation of milk increases its vitamin D content. Steenbock, now an emeritus professor on the biochemistry faculty, had proposed that WARF manage the applications of this discovery, and that the income be re-invested in UW research.

This has been done with great benefit, both to the world and the University. The Steenbock discovery has virtually freed the civilized world of rickets, a disease resulting from vitamin D deficiency.

Derived from the income of this patent and numerous others granted to WARF, and by the earnings of the foundation, WARF funds have made possible a large proportion of the University's world-renowned research programs.

In a recent report on the WARF contribution to Wisconsin research, Emer. Pres. E. B. Fred pointed out that the foundation's annual grants to the University have been especially valuable because they provide flexible support for research, give young faculty members a chance to demonstrate ability to conduct research, provide "venture funds" for promising projects in initial stages and additional funds to complete other projects, and afford a method for quickly allocating needed funds for urgent projects without red tape.

##

WIRE NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON, WISCONSIN 53706

5/8/64 jb

RELEASE: Immediately

MADISON, Wis.--Twelve contracts with federal agencies for services to be performed by University of Wisconsin departments, totaling $382,539.33, were approved by UW regents Friday.

The contracts include one of $94,411.50 with the National Aeronautics and Space Administration (NASA) for the UW Space Astronomy Laboratory in Madison to develop research on a satellite-borne instrumentation system.

Four contracts are with the Atomic Energy Commission: with the physics department, $45,000; Institute for Enzyme Research, $30,000; chemistry, $11,748; and zoology, $18,245.

Other contracts, amounts allocated, and departments assigned to the various projects:

With the Agency for International Development, $55,000, Agricultural International Program; Office of Naval Research, $42,155, statistics, and $36,026, journalism; U.S. Army, $23,100, plant pathology;

NASA, $19,999.74, Space Astronomy Laboratory; Department of the Interior, $2,300, state geologist; and Armed Forces Institute, $4,554.09, Extension Division.

##

U.W. NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON, WISCONSIN 53706

4/13/64 db

RELEASE: in PMs of Friday, April 17

BACKGROUND INFORMATION

(The following material has been prepared in conjunction with Dr. H. Gobind Khorana of the Institute for Enzyme Research at the University of Wisconsin. It is an attempt to assist journalists in gaining as wide as possible a view of the scientific facts and theories surrounding the announcement of the synthesis of short chain DNA molecules by Dr. Khorana and his immediate collaborators. It is hoped that this material will be useful to science writers as general background as well as a source of ready information for news stories concerning this recent work.)

Before entering into a general discussion of the chemical synthesis of DNA molecules, it seems appropriate to briefly go over some of the ideas and past findings that are currently accepted by virtually all scientists whose interests lie in the important yet vaguely defined field of molecular biology. These ideas, together with the problems that have arisen from them, provided the rationale that led to an attempt to develop methods for the synthesis of nucleic acids of known sequence.

A vast amount of experimental and theoretical evidence supports the notion that the overall picture of the existence and propagation of life can be represented as:

DNA (deoxyribonucleic acid)----→RNA (ribonucleic acid)----→Protein.

Broadly speaking, this lineup shows that the propagation of life lies in DNA, the long, spiraling chemical known to be the carrier of the genetic information, the molecular blueprints, in every organism. This information is passed on to RNA, a similar chemical. In effect, this transfer is a way of getting the genetic plans into a usable form; the passing of the blueprints from the architect to the construction engineer. The final step is the production of protein under the direction of RNA. It is the vast array of proteins that compose the vital structural and functional chemical that support life.

-more-

Proteins are made up of subunits called amino acids, some 20 of which are commonly found in nature. From the fact that there are apparently no chemical restrictions governing the order in which these units may be hooked together to form proteins, plus the fact that amino acid chains can grow to thousands of units in length, it can readily be seen that the number of possible proteins is so large as to become quite meaningless.

The nucleic acids (DNA and RNA), on the other hand, are composed primarily of four subunits called nucleotides. A nucleotide is a unit made up of a base, a sugar molecule and a phosphate group. When the base is attached only to the sugar (deoxyribose in the case of DNA) and the phosphate group is absent, the unit is called a nucleoside.

In the case of DNA, the bases (called as such not because of their geometric position on a nucleic acid chain but because of their chemical personality) are generally guanine, thymine, cytosine and adenine, usually abbreviated G, T, C and A.

In nature, DNA exists in the form of a long double helix composed of two chains of nucleotides with the sugar of one unit linked to the phosphate group of the next, the bases projecting off to the side. The bases in the adjacent strands bond together like rungs on a ladder. Because of their geometric structure the bases hook together in a certain way, T always bonding with A and C always with G. The linkage is accomplished by means of hydrogen bonding, which forms a weak yet sufficiently strong bond. Thus, if one of the strands had on it the bases ATTC, for example, the strand next to it would have the bases TAAG. This picture of DNA is known as the Watson-Crick model.

It is this arrangement of paired bases that make it possible for DNA to replicate itself. If the two strands separate, as they do at the time of cell division, the A-to-T and G-to-C bonding characteristics enable each nucleotide to attract a complementary nucleotide, thereby forming a double helix once again.

RNA was also found to have four bases, the same with the exception that T is replaced by another base called uracil, or U. The two are very similar, differing only in the absence of a small side group on U that is present on T. More than one type of RNA has been found to occur within living cells, the most important being messenger RNA, or mRNA. This molecule is, in effect, the template or gene copy that migrates from the nucleus of a cell, where DNA resides and where mRNA is formed, into the surrounding material (cytoplasm) where it directs the production of protein. mRNA is the complement of the information-carrying bases on a DNA strand--if the DNA base sequence was ATTC, the corresponding bases on the RNA chain would be UAAG.

Because of a lack of any similarity in the number or in the character of amino acids and nucleotides, it became obvious that no one-to-one, direct transfer of directions could exist. Thus, it was apparent that the sequence of bases on the nucleic acids must form some sort of a code.

The most attractive idea to come along was that a sequence of three bases, called a triplet, specified a certain amino acid. This would mean that there are more possible triplets than there are amino acids, but there was no good reason to suspect that a given amino acid couldn't be coded for by more than a single triplet. However, it is also possible that the code words are doublets, with the opposite character: A single doublets codes for more than one amino acid. Yet these possibilities are still just that--possibilities. It has not been definitely proven to date whether the code is in triplets, doublets, combinations of the two or even something else entirely.

The first major advance toward solving the code came some two years ago when it was announced that an enzymatically synthesized RNA chain composed entirely of U (consequently called poly-U) directed the formation, in the laboratory, of a protein composed entirely of a single amino acid, phenylalanine. This work opened the way for the first great assault on the amino acid code by hundreds of biologists around the world.

But there were strict limitations as to both the extent and the precision of this general method of decipherment. Most important was the fact that RNA chains consisting of more than one base could not be prepared in known sequence. This meant that exact information about the code could be found only up to a point. For example, if it is assumed for a moment that the amino acid, or genetic, code is in triplets, then it might be possible to show that a certain triplet--a code word--composed, say, of two U's and an A specifies a particular amino acid. However, it wouldn't be possible to establish with absolute certainty whether the actual triplet in this case was UUA, UAU or AUU.

In spite of these limitations, a great deal about the code has come to light. It appears, for example, that the code is degenerate, that more than one triplet (or doublet or whatever) codes for a particular amino acid. It may well be, however, that this apparent degeneracy results from knowing only the composition of code words and not the exact arrangement of code letters within them. Also, there has yet been no way of determining if there are breaks, or commas, between the code words.

To advance knowledge of the code beyond its present stage, one of two things must be placed within the control of scientists. Either (1) a way of precisely determining the lineup of bases along a natural DNA or RNA chain had to be developed, making correlation with the amino acid sequence possible, or (2) methods of synthetically constructing, or hand-tailoring, DNA and RNA chains of predetermined sequence were needed.

The first approach has thus far proven infeasible. It is relatively easy, though time consuming, to elucidate the amino acid sequence of a protein. Working out the order of nucleotides on a naturally occurring piece of DNA or RNA, however, simply cannot be accomplished by existing methods though new methods are now being developed. A protein can be examined by breaking many molecules of it into fragments and then identifying these. Different of these molecules break up into different overlapping fragments, with the result that a picture of what must have been the

original order of the amino acid is obtained. When this sort of technique is applied to nucleic acids, the nucleotides break mainly into non-overlapping fragments. Thus, while it is possible to find out what bases are present in a nucleic acid molecule and in what percentages, it is impossible to establish their order, at least on molecules longer than 20 nucleotides.

The second approach--synthesis--offers the investigator the advantage of having considerable control over his experiments. He would know with certainty the base sequence of the nucleic acids he was starting with and, after amino acids are put together into short proteins, he would need determine only the sequence of amino acids to find out the details of the code.

It is this approach that should be possible now with the utilization of the methods worked out in this laboratory. The methods have thus far been used to piece together a few short, single-stranded DNA models. RNA has not been made as yet because of technical difficulties, though it is expected these will be overcome in the future.

In principle, the chemical methods that have been employed to compose DNA of known sequence are simple. Two general types of reactions were used, both known to and used by chemists for decades. One is the selective protection and coupling of certain reactive sites on individual nucleotides one at a time. The other is polymerization, coupling many at a time.

Both the stepwise addition of nucleotides and polymerization of nucleotides were dependent upon the discovery of the proper coupling reagents. Several years of work have gone into the investigation of coupling reagents most suitable for each type of approach. The first to be found was an organic chemical synthesized for this purpose. This compound, dicyclohexylcarbodiimide, was the result of considerable labor. Later, another compound was discovered that would also act as the condensing agent in the preparation of synthetic polynucleotides. This one, mesitylene sulfonyl chloride, is a relatively simple organic compound and is easily obtained. It was literally discovered off-the-shelf. One or the other of the coupling agents are used in each step of a synthesis.

With the proper condensing agents in hand, it was possible to form short DNA chains by two approaches, both involving the selective protection of reactive sites on a nucleotide, chemically a relatively simple matter in this case, and the joining together of these protected nucleotides. Briefly, this protection is the reacting of a nucleotide with certain chemicals that will bind to, and therefore mask, various reactive points on the molecule. These protecting groups must have the properties of being undamaging and unhindering to reactive sites other than the ones, or one, it bonds to and of being easily removed at the will of the chemist. In many cases, the discovery of the right protective groups is difficult and requires a bit of hit or miss experimentation. With the nucleic acids, however, protective groups are known and are relatively simple. Using this technique, complex molecules can be made to join together in certain, proper ways, so long as the right condensing agents, conditions, catalysts, etc., are present.

Building a chain one nucleotide at a time, a process called stepwise addition, can, in theory, be employed to synthesize single-stranded DNA molecules of any desired order of bases and of any desired length. In practice, however, stepwise addition is limited at present to probably 20 units or so. The difficulties here are mainly those of separation. Each addition of a nucleotide to the growing chain is another chemical reaction, and between each step the chain must be separated from the reaction mixture and purified. As chains get longer, these separations become increasingly difficult. Chemists, however, are always working on means of improving technique and thus it is likely that it will eventually be possible to construct longer chains by this method.

Polymerization is the running together of preformed pairs of nucleotides joined by the means just described. This procedure is one of the most common in chemistry and has found particular importance in the chemical industry. Perhaps the best example of polymerization is the application of the process to ethylene, a very simple two-carbon organic molecule. Under the proper conditions of heat and pressure, ethylene polymerizes to form carbon chains thousands of atoms long, a

molecule called polyethylene. Any long molecule, for instance rubber, plastics, various synthetics and indeed proteins and nucleic acids are called polymers. DNA chains put together by this method are also limited to only a few bases because of unfavorable solubility-factors. When nucleotide pairs undergoing polymerization grow to chains of about 12 to 16 units, they precipitate out of solution and react no further.

Employing stepwise addition, synthetic DNA molecules composed of the repeating triplets TTC and TTH have been prepared, 12 and nine-bases long, respectively. The base H, hypoxanthine, is one that does not occur in nature but that can be used in place of G. It requires less protection than does G and is therefore easier to handle.

By means of polymerization, DNA chains containing the repeating doublets TC, TG and AG have been synthesized, the chains being six pairs or 12 bases long in each case. The polymerization of preformed triplets is under study.

Not long ago, it appeared that these methods for the synthesis of known-sequence DNA chains would be of only limited use in the exploration of the genetic code; the chains were too short. Recently, however, work in conjuction with Dr. Arthur Kornberg at Stanford University has shown that use of the enzyme DNA polymerase (discovered by Dr. Kornberg) makes it probable that long chains of DNA can be prepared from the short ones. In the one case tried so far, it was shown that a synthetic chain formed of the repeating doublet AT four to six pairs long (this, incidentally, is an arrangment of bases found in nature) forms, under the influence of DNA polymerase, a chain of the doublet TA (the complement) thousands of pairs long. This increase in chain length is due to a slippage mechanism.

Another enzyme, RNA polymerase, acts upon synthetic DNA to form longer chains of RNA. In the one case tried here thus far, DNA composed of all T, poly-T, six to 15 bases long was acted upon by this enzyme to form poly-A RNA 50 to 150 units in length. More important, this same poly-A RNA (the complementary base) is active in the amino acid incorporating system, forming a protein chain of the amino acid lysine.

The importance and implications of the chemical techniques reported here are obvious. It cannot be stated with absolute certainty, of course, that the artificial DNA will, via RNA, make proteins in every case. But the evidence does indeed point in that direction. These new chemical tools, then, are the best methods to date by which to attack the amino acid code. The methods, along with refinements bound to come as more workers take up investigations using synthetic DNA of known sequence, should result in the eventual, if not rapid, deciphering of the genetic code. Not only that. Much is yet unclear concerning the mechanism of replication of DNA, a mechanism absolutely vital to life. The ability to prepare model DNA chains may be the seed crystal that will precipitate the facts.

-0-

Dr. H. Gobind Khorana

Born--Raipur, India, 1922. Dr. Khorana received his undergraduate and graduate education at Punjab University, Lahore, India: B.Sc. 1943, M.Sc. 1945 (both degrees with honors). He received his Ph.D. from the University of Liverpool, England, in 1948.

After his doctorate, Dr. Khorana went for a year as a government of India post-doctoral fellow to the Eidgenossiche Technische Hochschule in Zurich and then, from 1949 to 1952, to the University of Cambridge as a Nuffield Research Fellow.

In 1952, he became head of the organic chemistry section of the British Columbia Research Council and the University of British Columbia in Vancouver. While at that institution, he gained international recognition for the synthesis of coenzyme A in conjunction with Dr. John G. Moffat. In 1958, he was given the Merck Award from the Chemical Institute of Canada for outstanding contributions to the fields of organic chemistry and in biochemistry in Canada. Two years later he was awarded the Gold Medal for 1960 in the field of pure and applied science from the Professional Institute of the Public Service of Canada.

Later that year he was invited by the University of Wisconsin to serve as a co-director of the Institute for Enzyme Research and as chairman of Section III, one of the three research groups at the institute.

He is widely recognized as one of the world's most advanced researchers in the organic chemistry of the nucleic acids and is a pioneer in the field.

-0-

Dr. T. Mathai Jacob

Dr. Jacob, 36, was born in Kaloor, Kerala State, India. He received his B.Sc., M.A. and Ph.D. (organic chemistry) degrees from the University of Madras.

Before joining Dr. Khorana's group at the University of Wisconsin in October 1961 he did 2½ years of post-doctoral work at the Indian Institute of Science in Bangalore and worked for a year each at the University of Toronto, Canada, and the Stevens Institure of Technology in New Jersey.

Dr. Malcolm W. Moon

Dr. Moon, 24, was born in Bradford, England, and took his undergraduate and doctoral degrees (organic chemistry) at the University of Leeds, Yorkshire, England. He joined the Institute for Enzyme Research at the University of Wisconsin November 1962.

Dr. Saran A. Narang

Dr. Narang, 32, was born in Dayalbagh, U.P., India. He received his M.Sc. from Punjab University and his Ph.D. (organic chemistry) from the University of Calcutta. He was a post-doctoral fellow at Johns Hopkins University for a year prior to coming to the University of Wisconsin in September 1963.

Dr. Eiko Ohtsuka

Dr. Ohtsuka, 28, was born in Sapporo, Japan. She received her Ph.D. (pharmaceutical chemistry) from Hokkaido University and came to the University of Wisconsin in April 1963.

###

U.W. NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON, WISCONSIN 53706

RELEASE: in AMs of Friday, April 17

CHICAGO, Ill.--A new procedure for removing phospholipids from mitochondria membranes was described in a paper by Drs. Sidney and Becca Fleischer and Anna Casu of the University of Wisconsin Institutes for Enzyme Research, Madison, at the Annual Meeting of the Federation of American Societies for Experimental Biology.

The mitochondrion provides the cell with most of its energy. Surrounding the mitochondrion is a membrane composed of proteins and phospholipids. Phospholipids play an active role in the enzyme actions of the mitochondrion, and by removing them, their role can be better understood.

The method described involves treatment of mitochondria with phospholipases, which destroy only the phospholipids in the membrane. The success of this method depends on a special mild wash procedure which removes the breakdown products such as fatty acids which inhibit normal enzyme action.

Solvent extraction, a previous method used to remove phospholipids from mitochondria, was also developed by Dr. Fleischer and his co-workers, but this procedure destroyed some of the enzyme activities so that many could not be restored.

This new procedure of removing lipids from the mitochondrian membrane may eventually be applied in other research where lipid extraction is used.

Within the mitochondria, ATP molecules are synthesized through a process called oxidative phosphorylation. In this process, simple food substance are oxidized, releasing electrons which are transferred along a chain of reactions until they are accepted by oxygen to form water.

-more-

Add one--phospholipids

The chain is composed of a series of enzymes arranged in a certain sequence and grouped into complexes that synthesize ATP. There are four known complexes along this chain, and each one is now known to require a specific phospholipid in order to function. The new washing procedure was used to show the need of phospholipid in the first complex.

The method made it possible to remove phospholipids from a specific site and thereby stop the function of the mitochondrion. When this particular phospholipid was restored to the site, the mitochondrion gained full recovery.

This study is part of a comprehensive program directed by Dr. Fleischer on the physiological role of lipids. This group is currently concerned with understanding the precise function of phospholipids in mitochondria, as well as surveying other enzymes or properties of membranes which require phospholipids for function.

##

U.W. NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON, WISCONSIN 53706

RELEASE: in AMs of Wednesday, April 15

CHICAGO, Ill.--Antibiotics are known for their life-saving qualities, but their role in research is often to interrupt life processes so these may be more easily studied.

A paper concerned with antibiotics as a tool in research was presented by scientists from the Institute for Enzyme Research at the University of Wisconsin, Madison, to those attending the Federation of American Societies for Experimental Biology meeting.

All living things obtain their energy from ATP, a molecule formed during one of the life processes--exidative phosphorylation. In this process, simple food substances are oxidized, releasing electrons which are transferred along a chain of reactions until they are used to produce carbon dioxide.

The chain is composed of a series of enzymes arranged in a certain sequence and grouped into complexes that synthesize ATP. Each complex in itself is capable of performing a series of reactions, many of which are still biochemical mysteries. The site of these reactions is the mitochondria, tiny organelles found in all living cells and constituting the energy-producing factories of the cells.

Antibiotics are capable of inhibiting various reactions along the chain of oxidative phosphorylation. How they do this is not entirely clear, but the effect is to break the chain into smaller parts which can then be more readily analyzed and described chemically.

-more-

It is easy enough to find antibiotics to stop the process of energy transfer by breaking the oxidative chain. The difficult task is to find what sites along the chain they affect. By using particular antibiotics, with known actions, the chain can be broken into smaller pieces at precise, calculated sites.

In a paper describing the particular sites along the chain where two new antibiotics seem to act, Wisconsin scientists Dr. Philip P. Witonsky and Diane O. Johnson present evidence that the uncoupling sites may lie between the electron transfer chain and the chain supplying the necessary electrons.

If this is so, there may be another complex set of reactions linking the chain of enzymes joining electron supply and electron transfer. If so, the reaction taking place in this sequence must be elucidated before biochemists will have a complete understanding of the cellular oxidative sequence responsible for the "spark of life."

###

U.W. NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON, WISCONSIN 53706

RELEASE: in PMs of Thursday, April 16

CHICAGO, Ill.--The conservation of energy during oxidative phosphorylation may be much greater than what was previously estimated, according to Drs. Archie L. Smith and Marc F. Hansen of the Institute for Enzyme Research at the University of Wisconsin, Madison.

Oxidative phosphorylation is the process that leads to the formation of ATP, source of the body's energy. Smith and Hansen were able to double the efficiency of ATP synthesis--six ATP molecules produced for every oxygen molecule instead of three ATP's that are usually observed.

Simple food substances, when oxidized, release electrons which are transferred along a chain of reactions until they are used in the production of carbon dioxide. The chain is composed of a series of enzymes arranged in a certain sequence and grouped into complexes that synthesize ATP.

Smith and Hansen increased the efficiency of ATP synthesis by reducing the substrate level, or the amount of material that is oxidized to liberate electrons. Their work was reported Thursday at the Annual Meeting of the Federation of American Societies for Experimental Biology.

The cell regulates the production of ATP by varying the substrate and oxidation levels. Smith and Hansen believe that the increased efficiency noted in this study more approximates what actually occurs in the cell.

To understand this situation, one might think of the closing of the fuel valve on an oil stove while opening the damper. The efficiency, measured in calories, is increased as a little of the fuel is completely burned by the greater supply of oxygen before more fuel is added.

Apparently the local concentration of ATP within the cell may regulate the rate of oxidation. Over-production of ATP may throttle down the mechano-chemical system of the membrane and gear the rate of power production to the demands of the cell.

###

U.W. NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON, WISCONSIN 53706

RELEASE: in AMs of Friday, April 17

CHICAGO, Ill.--Nearly all our energy comes from sugars which we get in food. One sugar in particular, called glucose, is necessary for every energy-producing process in the cell.

The adrenal gland manufactures several types of hormones which regulate metabolism or energy production by affecting the level of glucose which reaches the cells.

If the level of blood sugar or glucose falls below a certain point, the adrenal gland releases glucocorticoids, a group of hormones which act on proteins, converting them into energy-rich glucose molecules by a process called gluconeogenesis.

Many hormones are thought to work by creating or exciting new enzymes which enhance or speed up a reaction.

Studies conducted at the Institute for Enzyme Research at the University of Wisconsin, Madison, have shown that hydrocortisone, one of the glucocorticoids, can convert protein into glucose without the formation of new enzymes.

A paper explaining this research conducted by Drs. Paul D. Ray, David O. Foster, and Henry A. Lardy was presented at the Annual Meeting of the Federation of American Societies for Experimental Biology.

In this investigation, an antibiotic called actinomycin D was used to inhibit the synthesis of messenger RNA, a substance used to produce enzymes. Even in the absence of new enzyme formation, it was found that proteins could still be converted to glucose.

The actual mechanism involved in gluconeogenesis is still unknown. This study has shown that the primary function of glucocorticoids is not to increase the formation of cellular enzymes.

###

U.W. NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON, WISCONSIN 53706

RELEASE: in PMs of Thursday, April 16

CHICAGO, Ill.--Two papers describing some hitherto missing links of information about oxidative phosphorylation were presented Thursday by University of Wisconsin scientists to those attending a special session on oxidative phosphorylation at the Annual Meeting of the Federation of American Societies for Experimental Biology.

Oxidative phosphorylation is the name given to the overall series of reactions which lead to the synthesis of ATP--the molecule that supplies energy for all the processes of life.

This process is made up of two related events: the oxidation reactions that supply electrons for transferal along a chain of complexes that synthesize ATP. Each one of these complexes is in effect a series of reactions carried out by four to six protein molecules locked within the complex.

A very promising model of this system has been devised by David E. Green and his associates at the Institute for Enzyme Research at the University of Wisconsin at Madison. This model accounts for many of the observed chemical reactions in terms of structural details.

The first paper, by Dr. George Webster, explained where some inhibitors of oxidative phosphorylation act on the reaction series. Some chemicals are capable of stopping phosphorylation at various points along the chain of reactions leading to ATP formation. For this reason, they are used purposefully to break the chain so parts of it may be isolated and studied.

-more-

Add one--oxidative phosphorylation

Webster investigated the most commonly used inhibitors and pinpointed their sites of action within the complex. Once it is known where in the chain these substances act, they can be used as tools to separate the complex reactions into smaller, precise units for further study.

The second paper given at this session on oxidative phosphorylation described the work of Drs. Marc F. Hansen, Archie L. Smith, Joaquin Espada and Pauline Yang, all of the University of Wisconsin. They have isolated and studied one of the proteins that stimulates the reactions of the complex but does not work at the other sites.

Each complex has an associated protein that serves to transfer electrons from the complex to ADP which is then converted to high-energy ATP. This protein is called a coupling factor and it is one of the three that have been isolated at the Enzyme Institute.

###

Enzymes. Fish.

U.W. NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON, WISCONSIN 53706

RELEASE: in PMs of Wednesday, April 15

CHICAGO, Ill.--Studies of mitochondria--the energy-producting factories in cells--may lead to a better understanding of all cellular membrane systems.

The mitochondrion is a cellular organelle or compartment separated from the rest of the cell by a membrane. Studies of this membrane show it has many characteristics common to all cellular membranes--and further investigations may reveal a general plan which would explain how they all operate.

A study that supports this view was presented in a paper at the Annual Meeting of the Federation of American Societies for Experimental Biology. The paper describes the work of Drs. Richard L. O'Brien and Gerald P. Brierley of the Institute for Enzyme Research at the University of Wisconsin, Madison.

They have been studying how substances needed for the synthesis of ATP move in and out of mitochondria. Through some unknown process, mitochondria can control how much of each substance that is to be transported.

O'Brien and Brierley found that certain materials cross the mitochondrion membrane by what appears to be simple passive diffusion.

In an earlier study, Brierley and others found that some materials, such as magnesium, calcium, manganese and phosphate ions are actually forced or propelled through the mitochondrion membrane.

Such a process needs energy which appears to be supplied by the same high-energy compound that is also used to synthesize ATP. Still unanswered is the question of which activity--ATP synthesis, or ion transport--gets preference under different conditions.

-more-

Add one--mitochondria

Passive diffusion of substances is another characteristic which the mitochondrion membrane has in common with all cell membranes. Other similar features are: an inner and outer membrane with a fluid compartment in between; a membrane composed of a protein and phospholipid in a network arrangement; the ability to force substances into spaces having higher concentrations of that substance; and elementary particles embedded in the membrane layers which function to supply energy to move these substances.

###

Enzyme Research Inst.

U.W. NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON, WISCONSIN 53706

4/13/64 db-1

RELEASE: in PM's of Friday, April 17

By DENNIS BLAKESLEE

CHICAGO, Ill.--Methods now exist for the synthesis--in the laboratory--of small pieces of genetic material of any desired arrangment, it was announced here Friday.

Using their new techniques, researchers at the University of Wisconsin Institute for Enzyme Research at Madison have put together short, biologically active chains of DNA, the molecular carrier of genetic information, with predetermined sequences of bases, or code letters.

The announcement, which will provide the molecular biologist and the biochemist with a powerful new tool with which to make further strides toward the understanding of life, came at a session of the 48th annual meeting of the Federation of American Societies for Experimental Biology.

This ability to synthesize small DNA models of known base sequence is the result of some 10 years of exploration by Dr. H. Gobind Khorana, co-director of the Institute, and his collaborators. A paper describing the methods, and the molecules prepared using them, was presented by Dr. T. Mathai Jacob, a member of Dr. Khorana's current research group.

The availability of these methods for making hand-tailored DNA models will, in all probability, lead to the final steps in deciphering the genetic code.

This code, embodied in the DNA molecule, is the keeper of the chemical instruction, the genetic blueprints, inherent in every living organism.

-more-

Along a strand of DNA, four bases--the code letters--occur at regular intervals. These bases can assume any order, thus resulting in the formation of short code words along the strand. By means of intricate chemical steps, these words direct the order in which the amino acids, the 20 building blocks of proteins, are bonded together.

The arrangement of code words along a DNA chain, and therefore the number of possible proteins, is vitually infinite. It is this quality that allows life to exist in all its immense variation.

In recent years, molecular biologists have made great headway in solving this code, often called the amino acid code. But the physical and chemical techniques available today set an upper limit to these investigations. For example, it is at present impossible to determine the sequence of bases along a given sample of naturally occurring DNA.

Due to these limitations, it is not known for certain whether the code words are in triplets, sets of three bases, or in doublets--or perhaps in something else entirely. And, although it has been determined in some cases what code letters are present within a word, their order within the word is unclear.

Other questions remain unanswered. Can a single code word specify more than one amino acid? Are some code words nonsense words, coding for nothing at all? Are there breaks, or commas, between the words? In which direction along the chain is the code read?

The synthetic methods of Dr. Khorana and his co-workers provide a means of solving these puzzles. In the laboratory, model DNA chains of known sequence can be employed by known procedures to make chains of amino acids. These short chains, short proteins in effect, can be analysed with great precision.

The new procedures are not revolutionary. Rather they are sophisticated variations on time-honored chemical methods adapted to DNA synthesis.

Add two--DNA-one

Two approaches were developed. One is the addition of code letters one at a time to a growing chain. The other is the running together--a process called polymerization--of preformed pairs of code letters.

Both of these chemical pathways depend upon having available the proper condensing agent, a chemical that brings about the correct linkage between the letters. Dr. Khorana spent several years developing one such chemical. Later, another was discovered literally off-the-shelf.

By stepwise addition, two very short DNA models with repeating triplets of bases have been prepared. By means of polymerization, three models with repeating doublets were made, also very short. Thus far both of these procedures are limited to short chains, about 15 to 20 bases in length, by technical problems.

Though these man-made strands can never approximate those found in nature, which are generally thousands and hundreds of thousands of bases long, they are enough to break the code. And, as the evidence seems to indicate, the code is universal among all organisms.

###

Enzyme

U.W. NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON, WISCONSIN 53706

4/13/64 db-2

RELEASE: in PMs of Friday, April 17

By DENNIS BLAKESLEE

CHICAGO, Ill.--Elegant new chemical techniques, described here Friday, may soon push man closest yet to an understanding of the basic processes of life.

The methods, developed at the University of Wisconsin, will allow biologists to solve many vital mysteries of heredity and genetics by enabling them to hand-tailor biologically active, though very small, pieces of the ultimate genetic material, DNA.

The announcement is the result of some 10 years of exploration by Dr. H. Gobind Khorana, co-director of the Institute for Enzyme Research on the University's Madison campus, and his collaborators.

A paper detailing the techniques was delivered at the 48th annual meeting of the Federation of American Societies for Experimental Biology by Dr. T. Mathai Jacob, a member of Dr. Khorana's laboratory.

In recent years, chemists and biologists have conducted a major effort aimed at deciphering the genetic code. This code, they know, is built into the long, thin molecules of DNA that are the source of the chemical directions, the genetic blueprints, in every cell of every organism.

They know further that code words are formed by varying arrangements of four chemicals--the code letters--that make up a part of the DNA molecule. These code words give the orders that determine what proteins are manufactured in an organism. These proteins, in their infinite variety, are the all-important structural and functional chemicals of life.

-more-

But, though tremendous strides have been made, scientists have yet to find out, among other things, both the precise number and the precise order of code letters within a code word.

These new chemical tools however, present the biologist with a clear-cut way of gaining this information, and much besides. Essentially, they make it possible to put together short chains of code letters in any desired sequence.

Seeing what short proteins are manufactured by the directions contained in a known sequence of code letters could result in a detailed picture of the code words. These methods of making DNA are so new that very little work of this sort has yet been performed.

Dr. Khorana and his colleagues have not developed revolutionary chemical methods. Rather, they are sophisticated variations on time-honored techniques adapted to the synthesis of DNA.

Two approaches were developed. One is the addition of code letters one at a time to a growing chain. The other is the running together--a process called polymerization--of preformed pairs of code letters.

Both of these chemical pathways depend upon having available the proper condensing agent, a chemical that brings about the correct linkage between the letters. Dr. Khorana spent several years developing one such chemical. Later, another was discovered literally off-the-shelf.

By stepwise addition, two very short DNA models with repeating triplets of bases have been prepared. By means of polymerization, three models with repeating doublets were made, also very short. Thus far, both approaches are limited to short chains--about 15 to 20 bases long--by technical problems.

Though these artifical strands can never really approximate those found in nature, which are usually hundreds of thousands of units long, they should be enough to break the code. And, as the evidence seems to indicate, the code is universal among all organisms.

###

Research
Enzymes

U.W. NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON, WISCONSIN 53706

3/19/64 eh

RELEASE: Immediately

By EDWARD HAWLEY

MADISON, Wis.--A number of diseases (such as cancer) are essentially errors in the way certain cell components are combined to form the cell. Cellular materials of all sorts are made in the wrong amounts.

Under a microscope, this can sometimes be seen by the changed appearance of the cell. On the chemical level, this means that certain enzymes -- substances which promote chemical changes in the body -- are present in wrong amounts and proportions to one another.

A University of Wisconsin scientist interested in the problem is Dr. Robert L. Metzenberg, associate professor of physiological chemistry and a John and Mary R. Markle Scholar. He is interested in how the amounts of various enzymes in a cell can be controlled in living organisms.

"This problem has some practical importance," said Dr. Metzenberg, "because what any cell turns out to be, whether normal or abnormal, will depend on what enzymes it has in it or how much of each. A cell is controlled by the enzymes inside it."

He noted that most of the current understanding of how the amount of a particular enzyme is controlled in a cell comes from studies of bacteria. In bacteria a gene exists which will control every last detail of the architecture of an enzyme to be made, but will give no instruction about how many molecules of the enzyme are to be produced.

But he said there will be another gene, or genes, which will say nothing about architecture, but will be only responsible for how much of the enzyme is to be made.

-more-

"In other words," he said, "there is a division of labor among genes specifying the structure and the amount."

Dr. Metzenberg suggested that the next question for a researcher is: "Does this absolute division of labor hold for organisms more complicated than bacteria? That is, for organisms with more complexly organized chromosomes?"

Dr. Metzenberg works with a bread mold (Neurospora) which is more complicated than bacteria, but much simpler than human beings. In one way it is like humans in that it has highly ordered chromosomes.

Dr. Metzenberg has been examining the effects of a gene that apparently controls both the structure and the amount of the enzyme.

"Obviously, the situation is different than that which has been found in bacteria -- at least in the case of this one enzyme," he noted.

Currently, Dr. Metzenberg is working on the problem of pin pointing the nature of the changes in structure that are caused by this gene. He has found that this enzyme is normally in the form of a number of sub-units (probably four) which are loosely stuck together.

The whole molecule can be broken into its sub-units by a number of simple procedures. When the abnormal enzyme is broken into sub-units, these sub-units behave differently in an electric field than do those obtained from the normal enzyme.

As yet, the only actual chemical difference that has been found between the normal and abnormal enzyme is that the normal enzyme contains two different amino-sugars called glucosamine and galactosamine. The abnormal enzyme does not contain any glucosamine.

As to an interpretation of his findings, Dr. Metzenberg said a "tentative guess" is that the amount of the enzyme which the cell produces is controlled at least in part by the amount and nature of materials other than ordinary amino acids that can be added onto the main chain of amino acids which make up an enzyme.

##

Enzyme

WIRE NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

1/10/64 jb

RELEASE: Immediately

MADISON--Fourteen contracts with federal agencies, including one of $100,000 with the Atomic Energy Commission to carry out research titled "A Study of Fundamental Particles," were approved by University of Wisconsin regents Friday.

The UW department of physics will work with the Chicago Operations Office of the AEC in handling the fundamental particles project.

The 14 contracts totaled $386,620, covering various services provided by University departments.

Other projects, amounts, and departments:

With the Air Force Electronic Systems Division, $11,836, meteorology; Army Medical Research and Development Command, $30,400, medicine; Army ROTC Flight Training Program, $2,520 and $2,245, both with the military science department;

AEC, $60,000, Institute for Enzyme Research; $8,220, dairy and food industries; and $35,000, radiology; National Aeronautics and Space Administration, $8,945, Space Astronomy Laboratory; Office of Naval Research, $29,849, geology; U.S. Forest Service, $3,000, entomology; Geological Survey, $59,250, state geologist; Fish and Wildlife Service, $14,500, bacteriology; and National Science Foundation, $20,855, geology.

###

Research. Enzyme

U. W. NEWS FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

RELEASE:

9/5/63 eh Immediately

By EDWARD HAWLEY

MADISON, Wis.--Automation helps to build automobiles, mine coal, and drill for oil, but at the University of Wisconsin Medical Center, it is reaching into the health field.

Dr. G. Phillip Hicks, director of the bio-analytical research program for UW Hospitals, in collaboration with Dr. Walter J. Blaedel, professor of chemistry, has constructed a machine that will automatically analyze enzymes and their substrates in the blood. In many cases, machine analysis can begin directly with the sample of body fluid.

While over half the routine laboratory tests are already being performed by automation, Dr. Hicks noted that in conjunction with this a research and development program in automation is underway to make it possible to keep up with rapidly increasing demands for newer and more complex tests.

One of the newer clinical tests is the determination of enzymes in the blood. Enzymes are important because they are responsible for catalyzing every chemical reaction in the body.

It was pointed out that many enzymes occurring in the blood can be detected at relatively low levels or concentrations. When tissues are diseased or dying, the levels of enzymes in the blood stream frequently increase, and it is this increase that researchers are interested in measuring.

Some measurement techniques can establish which organs are defective, and may also be able to tell to what extent and how they are damaged.

-more-

Dr. Hicks said that enzymes could be used as an analytical tool to aid in treatment of patients. In the field of medical science in general, the use of enzyme analysis as a tool in diagnosis has increased greatly over the past five to 10 years.

But enzymes are difficult to work with, and it has required automation to make many enzyme analyses on a routine basis practical.

The machine itself works this way: 1) a circular tray holds 20 cups of diluted serum, which the machine can process in an hour; 2) the serum sample is measured and mixed with chemical agents by a pump to form a reacting mixture; 3) this mixture is delayed for a fixed time in a thermostatically controlled block, after which the rate of enzyme reaction is measured automatically; 4) the reaction rate is recorded on a chart; and 5) from this chart the laboratory technician can read the level of a particular enzyme in the blood.

"Enzymes are very unstable, will deteriorate rapidly, and their methods of determination are very demanding," said Dr. Hicks "That's why it is difficult to accurately analyze them by the traditional laboratory methods."

Enzyme determinations can be very specific, and that is why it is advantageous to use them in determining the amount of sugar or other chemical substances in the blood.

Increased accuracy with automated enzyme analysis is possible because many conditions such as time and temperature are more precisely controlled than can be done by manual laboratory procedures. And some enzymes are so complicated to work with, explained Dr. Hicks, that without automation, it would be impractical to analyze them.

"Of the hundreds of enzymes," said Dr. Hicks, "currently only four or five are being determined routinely in the laboratories. Development of this machine should help increase the number that can be analyzed."

He said, "Such a research program can pay direct dividends in patient care by making new tests available when needed and, in some cases, making available important tests on blood samples which are only in a 'research stage' and not generally available to patients in other hospitals."

###

FILE

Enzyme Res. Inst.

THE UNIVERSITY OF CHICAGO
Office of Public Relations
MIdway 3-0800, ext. 4424

63-203
4-19-63

For PMs MONDAY, APRIL 22, 1963

WASHINGTON--A team of Midwest scientists has discovered an array of tiny biological particles they believe play a vital role in transforming food into bodily energy.

The particles are so tiny--only a fraction of a millionth of an inch in diameter--that they can only be seen with the power of the electron microscope, and then only with very advanced new techniques.

Yet each is a highly-organized packet of intricate chemical components that help release energy from food molecules in the cell.

Two reports on the particles were presented at the 100th annual meeting of the National Academy of Sciences in Washington, D.C., Monday, April 22nd.

DR. HUMBERTO FERNANDEZ-MORAN, Professor of Biophysics at The University of Chicago, described his electron microscope studies of the particles at The University of Chicago and earlier at Massachusetts General Hospital.

He called the particles "elementary particles" of the mitochondria, which are known as the power plants of the cell.

DRS. DAVID E. GREEN, PAUL BLAIR, AND T. ODA, of the Institute for Enzyme Research of the University of Wisconsin, also reported on their correlated biochemical investigations to the Academy.

Dr. Green and his associates were able to isolate from mitochondrion-rich beef heart tissue what they believe are essentially the same "elementary particles" Dr. Fernandez-Moran observed in the intact mitochondrion. The Wisconsin scientists said their test tube studies established that the isolated particles were fundamental working units of the energy-transforming mitochondrion.

A NEW APPROACH

Detection of the mitochondrial particles opens up a new approach to one of the central problems of present-day medicine and biology--the transformation of energy in living systems.

Discovery of the new membrane particles required magnification powerful enough to make visible objects 100,000 times smaller than the human eye can see.

-more-

With the traditional light microscope, the eye can see objects magnified about 1,000 times. The mitochondria themselves are so small--about one to 10 microns, or a few thousandths of an inch long--that they are seen under the light microscope only as tiny grains or threads in the body of the cell. There are from 50 to 5,000 mitochondria in virtually every living cell.

The development of the electron microscope, which probes objects with electron beams instead of light, made it possible to study the mitochondria in detail.

They were found to be minute fluid-filled structures made of a double membrane--one forming an outer envelop, the other arranged inside in a series of deep folds. The membranes themselves are only a few molecules thick.

HOW IT WAS DONE

Dr. Fernandez-Moran devised electron microscope techniques that made it possible to study the mitochondrion and its delicate membranes in even greater detail.

He developed special microscopic vacuum chambers that protected the moist state of the minute sub-cellular specimens and employed liquid helium to freeze the specimens at a few degrees above absolute zero for better preservation of the fine structure.

Using these procedures and other technical refinements, Dr. Fernandez-Moran examined the mitochondrial membranes and found them studded with rows of tiny particles--somewhat like the seeds of a pomegranate. He estimates that there are from 10,000 to 100,000 of the particles in each mitochondrion, depending on its size.

The particles themselves are comparable in size to the smallest viruses. Each particle has two recognizable parts--a faceted head, about 100 Angstrom units in diameter, and a tiny cylindrical stem, about 50 Angstrom units long and 40 wide, that connects the head to the membrane. An Angstrom unit is one 254,000,000th of an inch.

Since the new particles were detected by Dr. Fernandez-Moran, they have been observed by other scientists, using similar techniques.

THE MITOCHONDRIA AT WORK

In the Wisconsin studies, Dr. Green and his colleagues found evidence that the particles they isolated play a basic part in the complex work of the mitochondrion.

The mitochondrion's job is to release energy from food molecules in the cell by oxidation, and to harness this energy in the chemical bonds of adenosine triphosphate, or ATP, the universal carrier of chemical energy for the body's needs.

This process of chemical transformation in the mitochondrion involves at least 70 different enzymes and co-enzymes, precisely arranged in a highly organized pattern. The enzymes are proteins that act as chemical catalysts; the co-enzymes are substances, like vitamins, that make it possible for the enzymes to do their work.

In their laboratory studies, the Wisconsin group found that each mitochondrial elementary particle contains a score of these enzymes and co-enzymes organized in a composite of four separate chemical complexes.

Using delicate biochemical techniques, they were able to separate the four complexes and put them together again, "like a jigsaw puzzle."

In the organized composite, energy in the form of electrons released from food molecules is carried on a "double track" through two complexes, then on a single track through the third and fourth, and in the process is coupled to the formation of ATP.

The entire sequence is called the electron transfer chain. This transfer of energy in a series of small chemical reactions avoids the sudden release of energy that would upset the even temperature of the cell.

ASSESSING THE FINDINGS

Commenting on the particles and their function, Dr. Fernandez-Moran said: "It seems only logical that nature would organize such a complicated enzyme sequence in a compact package."

He emphasized that the findings in the three-year joint studies have broad implications for the investigation of biological energy systems.

He pointed out that mitochondria belong to a large group of structures which are derived from cell membranes and which are known to have energy-transforming functions. The group includes chloroplasts in green plants, photoreceptors in the retina of the eye, and the myelin sheath that covers nerve fibers.

They are called "Lamellar systems" because they are made of thin layers of fatty protein membrane, similar to the membrane of the mitochondria.

The mitochondria are the first of this group that scientists have been able to isolate and study in detail in terms of the ultra-fine structure, chemical composition, and function of their membrane layers.

"In many respects, therefore," Dr. Fernandez-Moran said, "the mitochondrion can be compared with a Rosetta stone, the deciphering of which will ultimately permit us to decipher the molecular code of the energy-transducing systems in the living cell."

INVESTIGATOR'S BACKGROUND

Dr. Fernandez-Moran, an authority on electron microscopy, has been a member of the biophysics faculty at The University of Chicago since July 1, 1962.

Venezuelan-born, he was formerly head of the department of biophysics at the University of Caracas and the Founder-Director of the Venzuelan Institute for Neurology and Brain Research.

He came to the United States from Venezuela in 1958. Before joining the University of Chicago faculty, he held joint appointments for four years as Associate Biophysicist at the Massachusetts General Hospital and Head of the Mixter Laboratories for Electron Microscopy; Visiting Lecturer in the Department of Biology at the Massachusetts Institute of Technology; and Research Associate in Neuro-pathology at Harvard University.

He holds two M.D. degrees, one from the University of Munich, and the other from the University of Caracas. He earned the Ph.D. degree in Biophysics at the University of Stockholm.

# # # # #

BMH:jp

U. W. NEWS FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

4/19/63 jl

RELEASE: 3:30 p.m. EST Monday, April 22

WASHINGTON, D.C.--(Advance for 3:30 p.m. EST Monday, April 22)--Isolation of the specific cluster of molecules responsible for the unique capacity of living things to convert foodstuffs to utilizable energy was reported Monday by University of Wisconsin scientists to the National Academy of Sciences in Washington.

Prof. David E. Green of the UW Institute for Enzyme Research reported that a group of Wisconsin enzyme chemists has isolated the elementary molecular unit responsible for the oxidation of foods and manufacture of the molecular "storage batteries" known as ATP.

The elementary particles are found in cellular structures known as mitochondria, each of which contains some 15,000 such units in a long repeating chain. These units manufacture ATP from the substances formed by digestion of food, and the energy of ATP is then tapped by living cells to carry on life processes.

The mitochondrion aptly has been called the powerhouse of the living cell, for here the ultimate energy-tapping processes are carried on that give living things energy for muscular activity, organ and tissue function, even the thought processes of the living brain.

The discovery was disclosed by Prof. Green at the 100th annual meeting of the National Academy of Sciences, in a paper co-authored by P. V. Blair and T. Oda of the UW institute and H. Fernandez-Moran of the Massachusetts General Hospital, Boston, now professor of biophysics at the University of Chicago.

Green pointed out that the mitochondrial elementary particles can be likened to machines, each of which is a complete transformer unit for converting oxidative energy to chemical energy locked in ATP--the cellular storage battery.

-more-

"The elementary particle is a composite or mosaic of some 40 different protein molecules chemically fused or bonded together in a very precise and intricate fashion," he pointed out.

"Within the particle are a series of functional groups which undergo a cycle of reduction and oxidation. Electrons move in a definite sequence from one functional group to the next and coincident with the movement of electrons, ATP is synthesized," he added.

The electron microscope studies of Fernandez-Moran suggest a blueprint for the arrangement of the elementary particles in the mitocohondrion. Covering the periphery of the mitocohondrion and radiating into the interior is a membrane layer of protein and fat. The protein is known as the structural protein and this forms with phospholipid a continuous structure that might be compared to a spinal column.

"The elementary particles are attached to the spinal column of structural protein-lipid in paired arrays in much the same fashion that ribs are attached to the spinal column," Green explains.

In his address to the Academy, Green described the intricate chemical mechanisms by which this complex enzyme system performs its vital function, and also explains the methodology of isolation employed by the Wisconsin enzyme chemists.

The internal structure of the mitochondrion is barely recognizable when viewed through a regular light microscope, but the electron microscope investigations of Fernandez-Moran revealed "a world of detail" and he was able to recognize within the mitochondrion a repeating structure, spherical in shape, and about 10 times the size of a hemoglobin molecule, which he interpreted to be the elementary particle.

"The unit structure of the mitochondrion is thus made up of a continuous membrane layer overlaid and underlaid with arrays of elementary particles," Green explains.

In developing the isolation method, Green and his associates were thus faced with the difficult separation of membrane layer from the elementary particles. This they were able to do, however, and the resulting preparation of elementary particles was capable of carrying on the step in ATP-synthesis known as electron transfer, in which electrons are transferred from an enzyme known as DPNH to molecular oxygen.

This electron transfer is the final step in the process of oxidation of simple foodstuffs such as glucose which provides the energy needed by all living cells.

###

U. W. NEWS FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

4/5/63 vh RELEASE: Immediately

MADISON, Wis.--Two agreements pointing to participation in the space age head the list of 10 contracts between the University of Wisconsin and federal agencies and totaling $719,470 which the UW regents approved Friday.

Among those for service and research was a contract with the National Aeronautics and Space Administration for $183,000 to be administered by the UW Graduate School and to provide some 10 three-year fellowships distributed among basic, space-related science and technology studies.

NASA has provided funds to encourage such doctoral studies at a number of colleges and universities. Each fellowship offers $2,700 plus fees and tuition for each 12-month period.

NASA Research also is partner to the second space-related agreement, supplying $106,050 to the UW Space Astronomy Laboratory for a subcontract with the Cook Technological Center. The sum represents additional funds for construction of instruments which UW scientists will place on board an orbiting astronomical observatory. Launching of this is scheduled for 1964.

Other contracts with federal agencies approved by the regents include: Air Force Research, $12,664, meteorology; Atomic Energy Commission Research, three contracts--$13,374 chemistry, $21,880 minerals and metals engineering, and $28,000 Institute for Enzyme Research; Office of Naval Research, $30,218, chemistry; Peace Corps, $122,624, UW-Milwaukee Administration; and Department of Health, Education and Welfare, Office of Education, two contracts--$103,016, German, and $98,644 plus stipends, education.

###

U. W. NEWS FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

3/27/63 jl RELEASE: Immediately

By JAMES LARSEN

MADISON, Wis.--Scientists appear to be near the final elucidation of the intricate chemical pathways by which life obtains energy.

When this is accomplished, a third great barrier to full comprehension of the basic chemical laws governing life processes will have fallen.

The other two barriers have concerned the mechanisms of transfer of hereditary traits and the mechanisms for achieving harmonious control over the many and varied biochemical systems working together in the living cell.

A reasonably complete understanding of the fundamental principles involved in these two mechanisms has been achieved in recent years with the cracking of the DNA code and with the development of the concepts of feedback as applied to biochemistry.

The DNA molecules are constructed so as to form a template for construction of the proteins and enzymes of the living cell--and thus carry the "plans" for new life from parent cells to offspring.

Two University of Wisconsin scientists, Drs. Elizabeth and Waclaw Szybalski, have even demonstrated that it is now possible to affect repairs of genetically defective human cells in test tubes by merely bringing them in contact with extracts from normal cells--a process known as genetic transduction. In this process, "good" plans are exchanged for the defective plans in the certain proportion of the cells exposed.

-more-

The processes of feedback are now being studied in detail by scientists throughout the world. Discovery that the harmonious interaction of cellular biochemical processes is achieved by means of feedback--by which a chemical system can control its own activity--is now the basis for many advances in biochemistry and medicine.

It even appears that cancer may be the result of a broken link in a cellular feedback chain--or feedback chains--and this is the basis for much research now being conducted in the University of Wisconsin's McArdle Memorial Laboratory for Cancer Research.

The third great barrier to understanding life chemistry has been the method by which life obtains energy from the oxidation of foodstuffs.

Oxidation is usually a rapid--often explosive--process and one that generates heat of sufficient intensity to reduce any living thing to tinder. Yet the living cell accomplishes essentially the same thing in a well-controlled and orderly manner, shunting the energy into forms other than heat.

The wide variety of energy transformations that life can accomplish is quite remarkable. For example, muscles convert chemical energy into mechanical, the eye converts light energy into electrical, the nerve converts chemical energy into electrical, the ear converts sonic energy into electrical, the kidney converts chemical energy into osmotic, and a large number of others could be listed.

And basic to all of these, on a world-wide scale, is the transformation of light energy into chemical energy by green plants, in which production of sugar by photosynthesis forms the basic foodstuff upon which all life on earth depends.

During recent years, much of the mystery surrounding photosynthesis has been dispelled by scientists, and much has also been learned concerning the methods by which cellular oxidation is accomplished. Basic steps in each remain to be elucidated, but it appears that scientists must be very close to an understanding of both.

An intensive research program on the oxidation process has been carried on at the University of Wisconsin since 1947 when the Institute for Enzyme Research was established. The Wisconsin campus was an appropriate site for the new laboratory, for here much early work on the oxidation process had been carried on and a Wisconsin scientist, Dr. Van R. Potter, pinpointed the site of cellular oxidation in very small cytoplasmic bodies known as mitochondria. Another research team at Chicago accomplished the same feat at about the same time.

Once it was known that the mitochondria were the chemical powerhouses of the living cell, scientists at the UW Enzyme Institute under the direction of Dr. David E. Green embarked upon a program to see whether the basic process could be uncovered.

The mitochondria perform a key energy transduction in the living cell, producing molecules of ATP which serve as storage batteries, providing power for all of the other cellular functions.

In a complex chain of enzymes known as the electron-transport system, the energy from sugar is transferred to a substance, known as ADP, which is transformed to ATP in the process. Each ATP molecule contains a high-energy phosphate bond, and the chemical process is known as oxidative phosphorylation.

The energy required for the processes of life is obtained by the cell from the ATP storage batteries. The high-energy bond is tapped for its energy, and the ATP is transformed back to ADP which is then ready to be "recharged" into ATP by the electron transport system.

The chemistry of oxidative phosphorylation is unusually difficult to study in the laboratory because the delicate machinery--literally the machinery of life itself--is damaged irrevocably by the usual biochemical research techniques. Much of the effort of Green's group has been devoted to development of methods by which the cell's fragile chemical machinery can be studied.

-more_

add three--molecular biology

At the present time, work has progressed to the point where the fundamental molecular unit responsible for the electron-transport in the mitochondrion has been isolated, and the functions of the known components of the system--bearing such chemical names as cytochrome, flavoprotein, and coenzyme Q--have been elucidated at least in outline.

Green and four co-workers, Drs. R. M. Bock, Howard D. Tisdale, and R. S. Criddle, have also shown that a large mass of protein present in mitochondria, for which no specific task could previously be assigned, performs an extremely important function by providing a framework upon which enzymes and reacting organic molecules are held.

The discovery of this structural protein, as it is termed, constitutes a major step forward. It forces revision of many traditional notions of cellular enzyme action and now permits an attack upon what may well be the final barrier to understanding of the life-giving energy transforming processes of the cell.

A clue to the mechanics of this process has already been uncovered by Drs. Bock and Criddle, both members of the UW biochemistry department. They have found that the fundamental reactions of the electron-transport system are conducted by means of protein molecules with most unusual capabilities.

These molecules facilitate electron-transport by means of a flexible arm which carries or rotates a particular coenzyme into a position permitting subsequent reactions. Thus, it appears that legions of these protein molecules, acting in concert, carry on at least some of the key processes of oxidative phosphorylation.

Recently the Wisconsin scientists pointed out that the structure of the mitochondrial enzyme system and the physical forces involved in oxidative reactions seem capable of fully explaining the amazing ability of living organisms to transform energy from food into forms that can be used in muscular activity and physiological processes.

-more-

add four--molecular biology

The same system exists in essentially the same form in all living things--from the smallest bacterium to the largest mammal.

It seems apparent that the electron-transport system is a biochemical energy transducer common throughout the entire spectrum of life on earth.

"It would appear that once the problem of coupling electron flow to ATP synthesis has been solved in particular fashion early in evolutionary history, no major modification in the underlying principles was introduced thereafter," says Green.

While much remains to be learned about this basic biochemical process, it appears that enzyme chemists have at last hit upon what may be the key reaction in life's energy production system.

"Whatever the uncertainties," Green adds, "we can be sure on one point, namely that the mechanism of oxidative phosphorylation cannot elude us much longer."

###

file

Optical Diffusiometer for UW --
21-63

News release

ALLIS-CHALMERS
Milwaukee 1, Wisconsin

PUBLIC RELATIONS DEPARTMENT
Ronald Krysiek
SPring 4-3600, Ext. 3796

RELEASE: Tuesday, P.M.
January 22, 1963

MADISON, Wis., January 22 -- A 30-foot-long steel beam, fabricated by Allis-Chalmers with a fine watchmaker's precision, arrived here Tuesday after a cautious truck ride from West Allis to take part in a fascinating science detective story.

The "detectives" are University of Wisconsin scientists working at the internationally-known UW Institute for Enzyme Research. Their aim: solving some of life's basic mysteries.

The precision-built steel beam is part of an optical diffusiometer, a new model of a scientific detective tool quite unlike any other in the world.

-more-

FORM 7858
LITHO IN U.S.A.

add 1 -- optical diffusiometer for UW xx the world.

With it, researchers such as Dr. Louis J. Gosting will be able to more accurately measure and interpret diffusion. This is the process in which, for example, two different solutions of water and sucrose, placed in layers in a container, will naturally flow together until the solutions become one.

Dr. Gosting, an associate professor at the Enzyme Institute, is an expert on diffusion. With the instrument, he said, the diffusion coefficients of a substance will be obtained from measurements on a photographic plate to 1/1000th of a millimeter. That's way, way smaller than the thickness of a human hair.

Dr. Gosting said the diffusiometer will assist science to understand more thoroughly how substances are transported across the walls of a cell -- the smallest unit of life -- and within the cell itself.

This knowledge is expected to be helpful to chemical biologists at the institute. They regard life as a chain of reactions by enzymes, protein molecules that speed up a cell's vital processes. Daily experiments conducted with enzymes at the UW have led in the past to new understandings and better treatment of disease.

-more-

add 2 -- optical diffusiometer for UW xx of disease.

An optical diffusiometer works much like a camera. On one end of the steel beam will be mounted a light source assembly. In the middle will be a water bath container to hold solutions. At the other end will be a photographic plate.

Light will be shot through the diffusing solutions. Images formed by the rays as they pass through the solution will be recorded on the photographic plate, and later measured to produce scientific data.

The light source, water bath and photographic assemblies are being designed at present, Dr. Gosting said, and bids for their manufacture will be let soon by the university. He hopes to have the diffusiometer operating later this year.

If ever a piece of steel was babied, the beam shipped to Madison from the Allis-Chalmers plant certainly was.

"It weighs 5-1/2 tons," said Stanley M. Austin, assistant manager of the Allis-Chalmers Specialty Products Department, "but we took elaborate precautions to make sure it was delivered perfectly level.

"After all, machining the beam was a true watchmaking job for us -- we dealt with extremely close tolerances like 2000ths of an inch -- so we didn't want anything to happen during shipment."

add 3 -- optical diffusiometer for UW xx during shipment."

A special skid was made for the beam. Sections of two-inch-thick, high-pressure rubber hose were installed on the skid to absorb road vibrations. The beam rested on the hose sections and, in a sense, "floated" during its 85-mile trip along Highway 30.

As an added precaution, the truck was driven at reduced speeds, often as slow as 20 miles per hour. That's a snail's pace for Highway 30.

Installation Tuesday at the Enzyme Institute on University Ave. was equally as complicated. When a $600,000 wing was added to the building in 1960, it included a room 45 feet long and 10 feet wide to eventually house the optical diffusiometer. The room is in the basement, half a story below the level of a parking lot outside.

To get the 30-foot beam into the room, a window had to be completely removed from the building. Then the beam was carefully eased off the truck and rolled over blocking into the room. This took several hours.

Once inside, the beam was placed on its specially-designed steel supports, each weighing over 1,500 pounds. The supports, also supplied by Allis-Chalmers, feature air springs on which the optical diffusiometer will rest when fully completed.

Why air springs?

-more-

add 4 -- optical diffusiometer for UW xx air springs?

Less than 50 yards behind the Enzyme Institute is a railroad right-of-way. The air springs will insure that vibrations from trains rumbling past will not throw the sensitive machine out of alignment.

# # #

MADISON NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

7/25/60 ml

RELEASE: Immediately

Dr. D. Rao Sanadi, who worked at University of Wisconsin from 1951-55 with Dr. David E. Green's research group at the Institute for Enzyme Research, returns Friday, July 29 to speak on research he has been doing since he left UW.

Dr. Sanadi is now a section chief in the gerontology branch of the National Institutes of Health at Baltimore, Md. Gerontology is the study of the aging process.

He will speak on recent research in the mechanism of lipoic dehydrogenase. This is one enzyme in a complex series of enzymes known to exist in the mitochondrion, that part of the cell which supplies the body with energy.

Dr. Sanadi will speak in Room 101 of the Biochemistry Bldg. at 4:30 p.m. He is the first of a series of lecturers scheduled for 1960-61 and sponsored by the National Institutes of Health and under supervision of UW's Institute for Enzyme Research.

##

Enzyme Institute

WIRE NEWS

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

7/10/59 rt

RELEASE: Immediately

MADISON--Ground was broken on the University of Wisconsin campus Friday for a $600,000 addition to the UW Institute for Enzyme Research which will more than double the space in Wisconsin's unique research facility.

The institute is an international center of basic investigation into the nature and activities of enzymes, the only one of its kind in the world. It has no teaching responsibilities below the post-doctoral level, and concentrates on long-tem enzyme studies.

The new addition, a two-story 80 by 100 foot structure of cream brick, will be connected to the west side of the present building. Its construction and equipment are financed by a $300,000 grant from the National Institutes of Health and a $300,000 grant from the Wisconsin Alumni Research Foundation.

The original building was financed by WARF and Rockefeller Foundation grants, and much of the institute's work is grant-supported.

Completion of the structure will make possible the expansion of the present two research teams, one directed by Dr. David E. Green, the other by Dr. Henry A. Lardy, to a third major team plus some smaller groups, graduate Dean John E. Willard explained.

The addition will contain only limited office space; most of it will be taken up by laboratories.

The president of the University of Wisconsin Board of Regents, Carl E. Steiger, Oshkosh, mounted a bulldozer for a "modern" ground-breaking ceremony Friday.

The new building will be set back from University Avenue a considerable distance to avoid conflict with plans for widening this traffic artery.

Louis Siberz and Carl F. Huboi of the Madison architectural firm, Siberz, Purcell, and Cuthbert, are planning and supervising the new construction which will be modern in design, matching the original building.

###

5. (Contd.)

Electrical Work - Topp Electric Company, Inc., Madison - Base Bid	$40,689.00	
Deduct Alternates:		
E-2 (Electric work for storage shed)	225.00	
Alternate Bid (B) (Simplex fire alarm and clocks)	225.00	
Net Electrical Work Contract		$ 40,239.00.

(b) That the Executive Committee be authorized to act for the Board in the award of contract for the laboratory casework for the 1959 Addition to the Institute for Enzyme Research Building.

(c) That the following schedule of costs be approved for construction of the 1959 Addition to the Institute for Enzyme Research Building:

Construction Contracts	$498,410.00	
Architects' Fees	29,904.00	
Superintendence & Bureau of Engineering	6,000.00	
Electrical Conduit	15,000.00	
Construction Contingent	24,972.00	
Sub-total Construction	$574,286.00	
Equipment	25,714.00	
TOTAL		$600,000.00.
(Source of Funds:		
National Institutes of Health Grant - Construction	$287,143.00	
Wisconsin Alumni Research Foundation	287,143.00	$574,286.00
National Institutes of Health Grant - Equipment	12,857.00	
Wisconsin Alumni Research Foundation	12,857.00	$ 25,714.00
TOTAL		$600,000.00.)

U. W. NEWS FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

RELEASE:

4/11/59 rt

Saturday, April 11

MILWAUKEE--Final plans and specifications for a $600,000 addition to the Enzyme Institute on the Madison campus were approved Saturday by University of Wisconsin regents. Bldg-folder

The addition, to be financed with $300,000 provided by the Wisconsin Alumni Research Foundation and $300,000 provided by the National Institutes of Health, will more than double the size of Wisconsin's unique laboratory which is an international center of basic investigation into the nature and activities of enzymes. A research facility, the Institute also provides post-doctoral training for a number of specialists.

The addition, to be known as the Institute for Enzyme Research, will be attached by a corridor to the original structure which was built with an earlier grant from the Wisconsin Alumni Research Foundation plus funds supplied by the Rockefeller Foundation. The new portion, immediately west of the present building, will not interfere with the proposed relocation of University Avenue, University officials pointed out.

In other actions on University buildings and grounds Saturday, the Regents:

1. Approved final plans and specifications for the $165,000 Agricultural Shops, to be located at the intersection of Elm Drive and Observatory Drive extended, on the Ag Campus, the first of three wings of the building;

2. Let contracts to low bidders on a Farm Demonstration Home at the Ashland Branch Experiment Station and a Farm Service Wing on the Feed Storage Building on the Madison campus;

-more-

add one--buildings and grounds

3. Approved purchase of a $159,500 nuclear training reactor from the General Electric Co. with funds provided by the Atomic Energy Commission and empowered the University administration to apply to the State Building Commission for a $75,000 remodelling project in the Mechanical Engineering Building to house it;

4. Set a $12-per-year fee for faculty parking permits at the University of Wisconsin-Milwaukee and established a parking-meter area where students and others can park at the rate of ten cents for four hours;

5. Authorized use of $10,000 from the principal of the Bess G. Heath Fund for remodeling at Wisconsin General Hospital for the Respiratory Center there;

6. Set lot prices in the University Hill Farms--north hill addition ranging from $1,500 to $2,900, and amended restrictions on the parkway addition to allow swimming pools in that addition and in north hill;

7. Approved sale to the city of Madison of about an acre of land in University Hill Farms for the extension of Tokay St. for $3,402.

Contracts approved by the regents for construction of the Farm Service Wing on the Feed Storage Building included $29,300 to J. H. Findorff and Son, Madison, for general construction; $6,330 to Russell Structures, Madison, for a prefabricated steel building; $8,945 to Middleton Plumbing and Heating Co., Middleton, for heating and ventilating; $3,147 to Monona Plumbing Service, Madison, for plumbing; $2,719 to Topp Electric Co., Inc., Madison, for electrical work. Funds for construction were provided by a $58,000 State Building Commission appropriation.

Contracts approved for construction of the Farm Demonstration Home at the Ashland Branch Experiment Station included $12,659.50 to Wiezorek, Inc., Ashland, for general construction; $1,010 to Bauer Electric Shop, Ashland, for electrical work; $1,180 to Casperson Heating Co., Inc., Ashland, for heating and ventilating; $1,467.10 to Yankee Plumbing and Heating, Ashland, for plumbing. Its $20,000 cost will be met from a State Building Commission appropriation for Branch Stations.

###

WIRE NEWS

Enzyme Institute Laboratory & Research [illegible]

FROM THE UNIVERSITY OF WISCONSIN NEWS SERVICE, MADISON 6, WISCONSIN

3/15/58 rt RELEASE: March 15, 1958 Bldg. folder

MADISON--The Wisconsin Alumni Research Foundation has given the University of Wisconsin $300,000 to pay half the cost of a major addition to its Institute for Enzyme Research.

University regents accepted the funds Saturday. Earlier, the board had authorized application to the National Institutes of Health for $300,000 to provide the other half of the construction costs.

In another building action, the regents cleared the way for construction, beginning perhaps next month, of a major heating plant addition. They set up the legal framework for use of Wisconsin State Agencies Building Corp. funds to finance the $4,239,560 plant and confirmed their executive committee's authority to purchase seven additional parcels of land on North Mills, North Charter, and West Dayton Sts. for its location.

Owners and the parcels purchased included Otto Karl and Jeanne Ellen Kappel, 122 North Mills; Victor and Esther Blum, 120 North Mills; Mrs. Mary Devine, 1111 West Dayton; Amelia B. Ring, 1117 West Dayton; A.P. Schmitt, 1113 West Dayton; Mrs. Estella G. Kraemer, 135 North Charter; and Lee Stagner, 123 North Charter.

In other actions on University buildings and grounds Saturday, the regents:

1. Approved final plans and authorized bidding on a $30,000 soils laboratory addition to the Marshfield Branch Experiment Station;

2. Authorized their executive committee to award contracts for the two-million-dollar laboratory addition to Service Memorial Institutes, the Medical School building;

-more-

3. Authorized purchase of buildings and equipment of the Northwestern University Engineering Survey Camp at Taylor Lake near Cable, Wis., for $35,000, payable at the rate of $5,000 a year;

4. Approved preliminary plans and a location, directly east of the present Bulk Feed Storage Building, for a new Feed and Farm Service Wing;

5. Approved an $8,738 contract for purchase of granite for the Library Mall pool from the Cold Spring Granite Co., Cold Spring, Minn.;

6. Confirmed executive committee approval of a $23,970 contract with C.A. Hooper Co., Madison, for construction of steam service to the new Men's Residence Halls and Dining Hall;

7. Confirmed executive committee approval of the purchase of the property at 430 Lorch St., Madison for $9,500;

8. Approved sale of a tract of 81,700 square feet in University Hill Farms, commercial reserve addition, to Dairyland Managers, Inc. for $67,500;

9. Approved sale to the city of Madison of 10 acres of land for park purposes in the University Hill Farms, park addition, for $27,500.

The 10-acre plot sold to the city adjoins another 10-acre plot dedicated by the University to the city, without charge, for park and drainage purposes. The 20-acre park area will be in the block south of the area reserved for a new state office building and near the area reserved for garden apartments.

##

ENZYME INSTITUTE

Just across University Avenue from the First Congregational Church is the University's new Enzyme Institute, a three-story laboratory building of concrete and brick.

The financing for this building includes a $350,000 construction loan from the Wisconsin Alumni Research Foundation, and a $100,000 grant for special equipment from the Rockefeller Foundation. The Institute represents a pioneer step, since it is, within a university, a fundamental research center having no teaching responsibilities below the post-doctoral level. This is unique in the biological sciences within an American university.

Every effort is being made in the Institute to provide conditions for long-term work and progress through serious, systematic enzyme research without the interruptions of short-term temporary projects. The Institute is expected to become an international center of basic investigation into the nature and activities of enzymes, and as such will vastly enrich the possibilities of this University continuing to make significant health-giving research discoveries for the benefit of all mankind. The Institute will also contribute greatly to our output of highly trained teachers.