MINUTES

142nd MEETING

ADVISORY COMMITTEE FOR BIOLOGY AND MEDICINE
U. S. ATOMIC ENERGY COMMISSION

at

Brookhaven National Laboratory
Upton L.I., N. Y.

May 6-7, 1972

The 142nd meeting of the Advisory Committee for Biology and Medicine was held May 6-7, 1972, at the Brookhaven National Laboratory. Members present were Drs. R. D. Moseley, Jr., Chairman; P. R. Stout, Vice-Chairman; C. A. Finch, A. J. Haagen-Smit, T. A. Lincoln, J. B. Storer, Scientific Secretary, and Miss Rosemary Elmo, Executive Secretary. Headquarters personnel from the Division of Biology and Medicine included Drs. J. R. Totter, Director; D. Bruner, N. Barr, F. Brooks, R. Rabson, and R. Wood. Mrs. Gail Bradshaw was present from the Office of Information Services, Headquarters, as was Dr. John Harley, of the Health and Safety Laboratory in New York. Dr. Maurice Goldhaber, Director of the Brookhaven National Laboratory, welcomed the Committee and then turned the scientific program over to Dr. Victor Bond, Associate Director, who chaired the scientific session.

The first presentation was by Dr. George Cotzias who introduced his presentation by revealing areas of research emphasis in his program that had been followed in the past. These included studies on the metabolism of neuro transmitters and the metabolism of trace metals, especially manganese and zinc. Methods for analyzing trace metals by activation analysis have been refined to the point where they can now do non-destructive testing for the trace metals and then use the same sample to assay for neuro transmitters. Dr. Cotzias then went on to review the well known story of the treatment of Parkinson's disease by means of L-DOPA. He then discussed other possible applications of L-DOPA. There is apparently a report in the literature indicating that small doses are efficacious in the control of mammary carcinoma. Osteoporosis also responds to treatment by L-DOPA, probably mediated through the hypothalamus. He then described briefly the present status of his studies on Parkinson's disease. One problem that is not corrected by L-DOPA therapy is the righting reflex. Dr. Cotzias and his group have found that gamma hydroxybutyric acid markedly improves this reflex. They have also found that apomorphine is effective in the treatment of Parkinson's disease and there is some indication that metatyrosine may be useful.

In an interesting experimental study they have found that they can predict the sensitivity of animals to the toxic effects of L-DOPA by measuring their absorption of manganese. The rank order correlation coefficient is +0.86.

A continuing problem with any form of therapy for Parkinson's disease including surgery, is the risk of inducing diorientation in the patients. Conversely, physicians treating patients with disorientation by drugs apparently increase the risk of the development of Parkinson's-like signs and symptoms in these patients. This suggests that there is a great deal to be learned about the neuro transmitters and Dr. Cotzias and his group seemed to be principally interested in this area of research at the present time.

Following the presentation there was a very lively discussion of Dr. Cotzias' work.

The second presentation was by Dr. L. K. Dahl on the genetic and environmental interactions in hypertension. Dr. Dahl pointed out that the idea that salt might play a role in the development of hypertension is an old one. He and his group have been working on this problem since 1948. In 1952, they examined the salt intake in various societies around the world and found that there was an association between high salt intakes and hypertension. They then tested the hypothesis directly in rats and showed a cause and effect relationship. While they were able to induce hypertension in most of their animals by a high sodium intake, they found that in any of their groups of rats there were some animals who seemed to be completely refractory to the induction of the hypertension. Further, the extent of the increase in the sensitive animals was quite variable. Logically then, Dr. Dahl concluded that there was an important genetic component in the sensitivity to the development of high blood pressure. They then began inbreeding sensitive animals and resistant animals. By 5-7 generations of inbreeding there was a very wide divergence in blood pressures and sensitivity to the induction of hypertension. Dr. Dahl pointed out that other investigators inducing hypertension by other means have also uniformly found that about one-quarter of their animals were non-responders, suggesting a genetic component regardless of the method used for inducing the hypertension. Dahl tested his resistant and sensitive lines by renal clamping and by five other techniques and found that in every case the sensitive animals responded and the resistant animals were refractory. The group has run some genetic testing of the F_1, F_2 and backcross generations and found that F_1's and F_2's were intermediate responders and the backcrosses were intermediate between parent and F_1. In the above breeding scheme the resistant animals were mated with sensitive animals and the progeny were tested for sensitivity. On the basis of the genetic testing it is possible to estimate that between 2 and 4 genes only are involved in determining resistance sensitivity. Dr. Dahl has worked out a theoretical model based on the assumption that only 2 genes are involved and has plotted expected responses against observed responses. The agreement between observed and expected was reasonably good. He pointed out that human data also agree reasonably well with a 2 gene model.

More recently the group has become interested in the biochemistry of this hypertensive response. They have found that there are differences in the secretion of certain steroids in resistant and sensitive strains. While the total steroid secretion was the same in both strains, there were different ratios in some of the particular steroids being secreted. They have since found a similar difference in patients. A study of the genetics of this difference in steroid metabolism indicated that a single genetic locus is responsible.

Dr. Dahl's group then evaluated the role of the kidneys in the induction of hypertension by a high salt diet. Their data show that if the kidney from a sensitive rat is transplanted into a resistant rat, the salt will quickly cause a rise in blood pressure. On the other hand, if the kidney from a resistant rat is put into a sensitive rat, there is no change in blood pressure on salt loading. If a resistant kidney is transplanted into a hypertensive sensitive rat, the recipient responds by a drop in blood pressure.

The group is now beginning to study the genetics of cholesterol metabolism. Their preliminary evidence indicates lack of an association between sensitivity to hypertension and cholesterol level. Following Dr. Dahl's presentation, there was again an extended and lively discussion.

The next presentation was by Dr. Harold Atkins who gave an overview of the nuclear medicine program in the Brookhaven National Laboratory. Radionuclides of particular interest include ^{99}Tc, ^{127}Xe, ^{97}Tc and the short-lived isotopes including ^{11}C, ^{18}F, and ^{123}I. As one might surmise, there is an active program in improving the instrumentation for scanning for these various isotopes. They have found that technicium-labeled red cells can be used in patients to do spleen scans. There is a need, however, to damage the labeled red cells so that they become trapped in the spleen. There is relatively little of the nuclide localized in the liver which is a considerable advantage over the conventional colloidal methods. Undamaged labeled cells remain in the circulation and consequently it is possible to visualize the heart and major blood vessels very well. Dr. Atkins showed a particularly impressive picture of a defect in the carotid artery.

To visualize the kidney, they have used technicium-labeled DTPA. This material is cleared through the glomerulus but is not reabsorbed. Use of the labeled DTPA can also measure clearance rates from the plasma into the urine. Aortograms can be made and measurements of the extracellular space can also be made.

The ^{18}F is used principally to label amino acids to attempt to visualize the pancreas. ^{18}F tryptophane looks particularly promising. They have noticed, however, that there are marked differences in the ratio of the amounts localized in the pancreas and kidney as a function of species.

^{123}I is used for thyroid imaging and the very short half life and other physical characteristics of the nuclide make it very useful. In the past the use of labeled ^{123}I was limited because it was uniformly contaminated with I-124. They are now able to get the I-123 almost completely pure. In addition to its use in thyroid scanning, there is a potential use in labeling albumins.

Fluorescent transmission scanning of the thyroid by irradiating the thyroid with an Americium source which emits 60 kev gammas is being investigated in phantoms. The technique looks promising.

The instrumentation group now has a 3-inch diameter germanium crystal and a germanium scanning camera is being developed.

Dr. Stanton Cohn described studies on the neutron activation of the skeleton followed by whole body counting to estimate the various constituents of the skeleton. They use either 14 MeV neutrons from a conventional generator or the 4.5 MeV neutrons from a ^{238}Pu, Be source. As might be anticipated, a major problem is obtaining uniform fluences throughout the body. In terms of getting a uniform distribution of thermal neutrons which are the ones captured by the chemical constituents, 14 MeV neutrons give the best distribution. ^{252}Cf, being of very low energy, gives a rather poor result. At the present time they are using 14 50 curie sources of ^{238}Pu mixed with Be. A moderator is fit very closely around the patient's body to give uniform affluences of thermal neutrons. Calibrations have been worked out for the content of calcium, phosphorus, chlorine and sodium. The total radiation doses to the patients are about 300 millirem from the Pu, Be sources.

Diseases that have been investigated include a great variety of bone diseases such as osteoporosis, Padgett's disease, parathyroid dysfunctions and other hormonal dysfunctions. Calcitonin is used as a specific therapy for a number of these diseases and they find that they are able to measure the patient's response quite adequately using their activation method.

Dr. George Woodwell described some of the present activities of the ecology group. In the past they studied intensively one of the onsite forests. They are now interested in studying an estuary.

Their previous studies on the forest produced some interesting observations. One of the things they looked at was the carbon budget. Most forests or productive fields have a net production of about 200 grams of carbon per square meter per year. If one takes out the loss to decay and to animals, the net production in the forest they studied was about 500 grams per square meter per year. Mature forests, of course, come into an equilibrium and there is no net production of carbon.

In comparison to forests, estuaries are much more complicated because of imports and exports to the estuary. It is not known whether estuaries typically reach an equilibrium value. The group headed by Dr. Woodwell is presently studying Flax Pond which is relatively simple to study because there is no input by way of a river or stream running into it. It is simply a tidal pond connected to Long Island Sound. Woodwell pointed out that it is commonly believed that estuaries are very productive in terms of producing organic matter. His studies suggest that this is not so. They have studied the exchanges with the ocean and most of the exchange is in the form of dissolved organic material. This amounts to 1-12 mg per liter, while small particulate materials amount to about 1/10th of this. They find that by studying the input from and the output to the ocean, they

can estimate the net production in the estuary. Curiously there is more organic material coming into the estuary from the ocean than goes out. This means that the material must either be respired or sedimented.

They are also looking at the sulfur budget of the estuary and find that the estuary takes sulfate from the ocean and releases it to the atmosphere as sulfide.

The fish populations of the estuary vary enormously being by far the highest in the summer and fall. A great variety of species are present with the concentration of fish being thousands of times higher than it is in Long Island Sound. His conclusions were that the estuary is a carbon sink. Its respiration is very high. Based on this he concludes that the estuary is in fact cleaning the waters of Long Island Sound and additionally that in effect the estuary serves as a feed lot for fish.

Dr. F. W. Studier reported on his studies on the genetics of T-7 bacteriophage. The T-7 is a very small phage consisting of a single molecule of double stranded DNA. It codes for 25 to 30 proteins. Studier has undertaken to identify all the proteins associated with the various gene loci. In order to do this he has collected a few thousand mutants principally of the amber, temperature sensitive, and deletion type. By manipulating these mutants, and by some refinements in gel electrophoresis, he has been able to identify 22 of the proteins associated with the known gene loci. According to Dr. Studier the amount of protein equals the coding capacity of the T-7 phage DNA.

Dr. B. P. Schoenborn described neutron diffraction studies of molecular structure. He pointed out that while x-ray diffraction has been used extensively, it is not entirely satisfactory because of the low scattering ability of the light biological molecules. For example, it is not possible to see hydrogen. In contrast, the scattering by neutrons is a function of the element and is not related to its atomic weight. By using Fourier transforms, he is able to see hydrogen in a molecule as a negative contour. Nitrogen also shows up very well. In general neutron diffraction has been very useful in distinguishing large molecules. Their particular interest has been in the examination of membranes, ribosomes and other cellular components and from their studies they can infer something of the structure of these organelles. When anesthetics are applied to membranes, they appear to disorder the structure. One problem with this technique is that high neutron fluxes are required.

Dr. M. Isaacson discussed plans for building a high resolution transmission scanning electron microscope. He apparently had previously been associated with the group at the University of Chicago that has built a somewhat smaller machine. The Chicago scope operates at 30 kev, has a resolution of 5 A and can detect atoms down to Z=80. Dr. Isaacson proposes to build a scope that would operate at 100 kev, would have a 1.8 A resolution and could detect atoms as low as Z=30.

The final scientific presentation was by Dr. D. Manowitz, of the Department of Applied Science. Dr. Manowitz is with the Meteorology group which has recently been transferred to this department. Their work in the past has been concerned with the dispersion of plumes from smokestacks and they have examined in detail the kinetics of the dispersion for distances up to 10 kilometers. At the present time they are extending the range of their studies up to 100 kilometers. Dr. Manowitz pointed out that existing equations for estimating concentrations in plumes as a function of distance are not adequate because they do not take into account wind shear, turbulence and certain other variables. The effect of these variables becomes increasingly important with increasing distances from the release point. They are trying to improve prediction equations. This has required the development of very sophisticated instrumentation to enable the tracking of very small quantities of sulfur hexafluoride and particulates at long distances from the release point. The sulfur hexafuloride of course is not a naturally occurring component of stack effluents but is injected into the source plume as a tracer. The group is also investigating the problems associated with plumes that might be released from nuclear reactors sited off-shore. There apparently is the real possibility that the on-shore sea breezes might bring the plume directly in and that it might be very narrow. This, of course, would result in high concentrations within the plume itself. An additional area of study concerns the rate of oxidation of sulfur dioxide in plumes. If it oxidizes this, of course, influences the concentration with time and distance. One of the reaction products, unfortunately, is very likely sulfuric acid but the rate of this reaction may very well vary with atmospheric conditions. Ammonium sulfate has also been identified as a reaction product from the sulfur dioxide.

This concluded the scientific presentations and the Committee recessed for the day.

The Committee reconvened at 7:20 A.M. for its executive session. Dr. Robert Conard, who for years has headed the team that periodically examines the natives on Rongelap who were accidentally exposed to fallout radiation, reported that this year his team was not permitted to examine these people. A representative in the Congress of Micronesia named Mr. Balos has charged that the United States is using the natives as guinea pigs, is more interested in the effects of the radiation that in treating the patients, and that the U.S. has been less than generous in its financial settlements with the natives. He was able to exert sufficient pressure to intimidate the Rongelap people into refusing examination. This seems very unfortunate because Dr. Conard and his team bring to the natives a level of medical care otherwise unavailable to them. Mr. Balos was aided and abetted in his attack on the U.S. by some left wing Japanese scientists and observers who had come to the islands to see the natives. It is not at all clear whether or how this problem will be resolved. The natives and particularly those with hypo function of the thyroid gland need continuing surveillance. With the

natives returning to Bikini it is imperative that a medical team keep all of these people under surveillance.

Dr. Totter reported that pressures are now being generated to return the natives to the Eniwetok Atoll which is in much worse condition than Bikini was. Surveys of the Atoll will be conducted by the Division of Operational Safety.

It was not clear that any action was required of the Committee and no recommendations were developed.

The Committee met with Dr. Victor Bond to discuss problems associated with the Brookhaven Divisions for which he has responsibility. Dr. Bond pointed out that there were extreme difficulties in maintaining good programs particularly in the area of medicine. In the mid-1960s the Medical Department had a professional staff of 47 while today it is only 32. Dr. Bond felt that this approached the minimum size that would be viable. He also argued that in the present climate of emphasis on relevance to mission, excellent programs such as those described by Cotzias and Danl could not be initiated. He felt strongly that particularly in medicine the staff no longer had the freedom to follow exciting new leads. This, of course, makes it difficult to recruit good people when such freedom is curtailed. It also creates a serious morale problem. In an effort to improve the funding situation they have tried to get increased outside support from agencies such as the NIH but because of the cost sharing requirements, it is very difficult to establish research grants with such agencies. Dr. Bond was frankly pessimistic about whether the Division of Biology and Medicine's medical programs could survive.

Dr. Moseley suggested that the Commission should talk with the people in NIH to try to resolve the question of cost sharing with non-government funds. In effect the present rules prevent the NIH from putting money into places already staffed with excellent people, fine equipment, good space, etc. The Committee discussed this suggestion and agreed that the ACBM should urge the AEC to try to get the legislation changed so that the cost sharing requirement by national laboratories could be avoided.

Dr. Totter felt that the national laboratories were not always treated fairly by the NIH panel system. Since the panels are dominated by university affiliated scientists, he felt there was a confusion of what the national science effort should be arising from a desire to help support universities and education. Dr. Totter felt that the national science effort should be clearly distinguished from any effort to support education in the universities. This led to a rather lengthy discussion of the problems of research funding. Dr. Stout took the strong position that if research is to survive in the U.S. it will survive principally in the national laboratory enclaves. Dr. Lincoln was particularly distressed that excellent medical programs such

as those described by Drs. Cotzias and Dahl could not be adequately supported. He felt the Committee should strongly endorse such programs. There was general agreement among the members that programs such as those of Cotzias and Dahl are excellent and extremely important to the national interest.

—In his concluding remarks to the Committee Dr. Bond pointed out that outside support amounted to about 10% of the budget in the Biology and Medical Departments. He felt that if the facilities and groups were to be maintained especially in the Medical Department, something drastic must be done at very high levels.

Dr. Bruner briefed the Committee on the potential availability of Pu^{236} and Pu^{237}. These two isotopes have short half lives and can be easily detected by gamma counting. The principal usefulness visualized would be in animal experimentation although some quantities might be used in soils and experiments with plants to study transport. Because of the short half life there is not a problem with persistent contamination. If there is sufficient interest in obtaining these isotopes, DBM will approach the Division of Research to determine whether they can be made available.

Dr. Bruner then reported to the Committee an episode involving an overdose of radiation that occurred in Detroit. A 68 year old woman had a Mucinous cystadenoma removed surgically but during its removal the cystadenoma broke and seeded the peritoneal cavity with metastases. The tumor board of the hospital recommended intracavity therapy with chromic phosphate. Through an error, sodium phosphate (the phosphate being radioactive with P^{32}) was given. The total dose amounted to 30 mc. Sodium phosphate, of course, is easily absorbed from the peritoneal cavity. The woman died four weeks later and the death certificate showed metastatic cancer and pulmonary infection. No autopsy was performed. A radiological physicist in the hospital found the error in the records and reported it to the Division of Compliance. Dr. George Thomas was requested to investigate. The clinical records showed that the woman had anemia, severe leukopenia, and bleeding into the intestinal tract. The conclusion was that this was a radiation death. The bone marrow dose was estimated to be between 600 and 900 rads. The AEC license to the hospital has been revoked but Compliance apparently is in a quandary as to what to do next. No action was requested of the Advisory Committee.

Dr. Bruner then reported on the activities of the United Nations Scientific Committee on the Effects of Atomic Radiation. The final drafts of reports on seven subjects have been prepared and the document will run to approximately 350 pages. During the deliberations on these documents, the physicists apparently argued strongly for use of the man rad concept while the biologists were generally opposed to this concept. Some sort of a compromise was reached and the concept is apparently somewhere in limbo. Dr. Bruner showed a couple of interesting tables that will appear in the report. The first of these had to do with levels of ambient radiation.

These levels are as follows: From natural radioactivity, 100 mr/yr; from medical exposures, 50 mr/yr; from fallout radiation, 1 mr/yr; from nuclear power activities, 1 mr/yr at the perimeter of the power station; all other sources of radiation, less than 1 mr/yr. Dr. Bruner indicated that the estimates of somatic risk are now somewhat higher than those arrived at previously but the estimates of genetic risk were somewhat lower. For example, in a population exposed to 1 rad, it is expected that there would be 30,000 naturally occurring genetic defects per million offspring. The radiation exposure would induce 20 per million in the first generation and an additional 280 in the F2 through F50 generations.

Dr. Totter discussed the fiscal 73 budget briefly. The Division is requesting 94.5 million but he felt that even if they obtain this amount which represents a modest increase, the funding prospects are grim because of cost increases and directed research programs. Dr. Totter reported that the hearings in the House and Senate went reasonably well although both Rep. Joe Evins and Sen. Ellender sharply questioned the wisdom of continuing the studies of the Atomic Bomb Casualty Commission. The Committee's position on this point is that the ABCC studies are invaluable and represent the best opportunity for learning about the effects of radiation in a human population. This population is unique and it is certainly hoped that it could never be duplicated.

Dr. Totter then discussed some of the reorganizations that have been going on within the AEC. The regulatory side of the Agency has been reorganized into three directorates. The directorate under Les Rogers has sent the Division a long list of questions needing answers and the DBM staff will try to initiate the appropriate research to obtain these answers. Mr. H. C. Bron, who was formerly Assistant General Manager of the Commission, has left and gone to industry. A new division has been split out from the Division of Research called the Division of Controlled Thermonuclear Research. This move apparently was made to emphasize the Commission's interest in fusion power. Mr. Julius Rubin has been named Assistant General Manager for Environment and Safety. It is not clear how this operation will interface with the Division of Biology and Medicine. Under Mr. Rubin is a new Division of Environmental Affairs to be headed by Mr. Robert Catlin. Again, it is not clear how this Division will interface with the extensive environmental research program in the Division of Biology and Medicine.

Dr. Totter then reported briefly on a conversation with Chairman Schlesinger. During the course of the conversation the Chairman asked whether an increase in DBM's budget of 30 million would permit it to broaden its programs sufficiently to encompass energy generation in general rather than solely nuclear generation. To respond to this query, the Division approached the national laboratories for suggestions on what research was required to give a balanced program in the biomedical effects of energy generation. The laboratories sent in a stack of paper precisely 42-1/2

inches high. Dr. Nat Barr put this material together in a very condensed form showing three different options requiring different funding levels. Members of the Advisory Committee have been provided with copies of this document. Dr. Barr described the approach used and discussed the document with the Committee. The brief document had been submitted to the Commission and it will be shown before the Office of Management and Budget within a week or so.

Dr. Totter reported that a planning document is due by the end of June showing DBM's plans for the next 7-8 years. It will be a requirement to show how new research would be phased in, some old research would be deemphasized, etc.

Dr. Totter then discussed his proposed reorganization of the Division. The principal change would be that the Ecological Sciences Branch and the former Fallout Studies Branch now known as Earth Sciences Branch would fall under a new assistant director for environmental sciences. The Civil Effects Branch formerly headed by Joe Deal has disappeared and Mr. Deal has moved to the Division of Operational Safety. A new branch will be created under Dr. Barr as Assistant Director. This branch will be known as the Evaluation and Analysis Branch and would have its function staff work to provide analyses on data generated in the various DBM programs.

DBM has been directed to get its story to the public better than it has been done in the past. Dr. Barr has been assigned this responsibility.

It appears that the name of the Division of Biology and Medicine will be changed to the Division of Biomedical and Environmental Research. The Division of Technical Information is now under John Harris as the Office of Information Services and there will be increasing emphasis on public information.

The Committee discussed the advisability of splitting biomedical and environmental research in the reorganization and concluded that this would be very unwise. The Committee felt that the proposed reorganization of the Division would improve effective cooperation between and among these various disciplines.

The Committee then discussed the letter to the Chairman.

The Minutes of the 141st meeting were approved as distributed. The Committee adjourned at 11:30 A.M.

Respectfully submitted,

John B. Storer

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