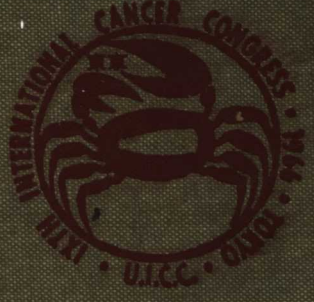
NINTH INTERNATIONAL CANCER CONGRESS

Abstracts of Papers



TOKYO

23rd to 29th, October, 1966

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CANCER CONGRESS

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Central Office:
Ninth International Cancer Congress
c/o Cancer Institute
Nishisugamo 2-chome, Toshima-ku, Tokyo, Japan

NINTH INTERNATIONAL CANCER CONGRESS

Under the Auspieces of

the

International Union Against Cancer

(*President: Sir Alexander* HADDOW)

With the Co-operation of

the

Science Council of Japan

(*President: Dr. Shin-ichiro* TOMONAGA)

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THE MOLECULAR BASIS OF TRANSLATION OF THE GENETIC MESSAGE

Severo Ochoa

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Genetic Expression

The genetic information of living organisms and DNA viruses is contained in one of the two DNA strands. It is transcribed transfer to a special messenger RNA through a DNA-directed synthesis of messenger. This RNA is an exact replica of the DNA strand that bears the genetic information and it programs the synthesis of proteins with features specified by the original DNA blueprint. Genetic and other experiments show that a linear sequence of deoxyribonucleotides in DNA specifies a corresponding sequence of ribonucleotides in messenger RNA and this in turn directs the synthesis of polypeptide chains with an unique sequence of amino acids. Thus, the four character (the four nucleotide bases) language of nucleic acids is translated into the twenty character (the twenty amino acids) language of the proteins.

Genetic Code

Clearly a linear sequence of several nucleotide bases must specify each of the twenty amino acids. A doublet code (two bases for one amino acid) would be insufficient to specify twenty amino acids for it would have only $4^2 = 16$ doublets, but a triplet code, with $4^3 = 64$ triplets, would contain enough information. There is evidence that the genetic code is a triplet code. Moreover, the code is non-overlapping and commaless. This means that in a sequence ABCDEFGHI.....XYZ, ABC would specify one amino acid, DEF another one, and so forth.

Molecular Mechanism of Translation

Assembly of the polypeptide chains of proteins takes place on the ribosomes as they move along the messenger. The amino acids are taken to the site of synthesis in an activated form linked to special transfer RNA molecules each of which is specific for one of the twenty amino acids. Their alignment in a sequence prescribed by the nucleotide sequence of the messenger depends on the recognition of the various base triplets of the messenger (codons) by triplets of complementary base sequence (anticodons) of the amino acid-carrying RNA's. Codon-anticodon recognition and interaction are believed to occur through a Watson-Crick base pairing mechanism.

Deciphering of Genetic Code

Cell-free systems of protein synthesis can be obtained from bacteria, reticulocytes, and other cells. They consist of ribosomes and supernatant fluid. The latter contains, among other things, various soluble enzymes required for the process. When supplemented with transfer RNA's, ATP, GTP, and messenger RNA these systems synthesize proteins characteristic of a given messenger, e.g., viral coat proteins, when viral RNA messengers are used. Natural messengers can be replaced by synthetic polyribonucleotides of known base composition. Poly U directs the synthesis of polyphenylalanine, poly A that of polylysine. Random polynucleotides such as poly UG, direct the synthesis of peptides containing phenylalanine, cysteine, valine, lysine and tryptophan among other amino acids. These observations opened the way for deciphering the genetic code for they showed that UUU and AAA are phenylalanine and lysine codons, respectively, whereas triplets containing 2 U and 1 G or 2 G and 1 U are codons for cysteins, valine, glycine, and tryptophan. With use of a variety of

synthetic polynucleotides, the base composition of some fifty codons was established two years ago. Clearly there is more than one codon for each amino acid indicating redundancy of the genetic code. The base sequence of the individual codons has been recently established by studies of (a) the specific binding of aminoacyl-transfer RNA's to ribosomes in the presence of trinucleotides of known base sequence, and (b) the synthesis of polypeptides with artificial messenger polynucleotides of alternating base sequence. For example, poly $(UG)_n$ with UGU and GUG codons, promotes the synthesis of polypeptides containing strictly alternating cysteine and valine residues.

Polarity of Translation

Since polynucleotide chains have a polarity, it was of interest to know the direction in which the messenger RNA chain is read during translation. This question has been answered with use of short polyadenylic acid messengers with an unique triplet of known base sequence at either end of the chain. For example, polynucleotides such as AAAAAA.....AAAAAC direct the synthesis of polypeptides of the structure lysine-lysine.....lysine-asparagine with NH_2-terminal lysine and COOH-terminal asparagine (lysine codon, AAA; asparagine codon, AAC). Since polypeptides are assembled from the NH_2- through the COOH-terminal end, the above results unequivocally establish the direction of reading of the message. The same conclusion has been reached from experiments on hybridization of insertion-deletion mutants of T2 bacteriophage affecting the synthesis of the phage-induced enzyme lysozyme. Other experiments indicate that the ribosomes start the reading of synthetic polynucleotide messengers at one end of the chain (the so-called 5'-end) and that this start sets the reading frame.

Beginning and End of Translation

Synthesis of natural polypeptide chains appears to require signals for initiating and terminating translation of individual cistrons. Initiation involves codons that direct the introduction of N-formylmethionine as the first (NH_2-terminal) amino acid of the polypeptide chain. Termination involves release of the completed peptide from the ribosomes preceded or followed by elimination of the transfer RNA attached to the peptide chain. The fact that certain mutations give rise to premature release of unfinished polypeptide chains suggests the existence of special codons for chain termination.

L 1

VIRUSES IN CARCINOGENESIS

Renato Dulbecco

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The main objective of this lecture is to critically evaluate the state of our understanding of the process of cell transformation by tumor-producing viruses. The work carried out during the last several years with the most suitable model systems, namely the RNA-containing Rous sarcoma virus and the DNA-containing polyoma, SV40 and adenoviruses, has led to conclusions of remarkable uniformity. The main outcome is that the transformed cells do not contain infectious virus but do contain some functional viral genes. Hence the conclusion that a defective viral genome is present in the transformed cells.

Another remarkable similarity is that in all cases the defect concerns the synthesis of the outermost coat of the virions.

These findings raise a number of important questions. The most crucial question is whether the presence of the defective viral genome is required for maintaining the transformed state of the cells. The mere presence of functional viral genes does not prove that they are required all the time. Conclusive evidence on this point can only derive from studies in which the function of the viral genes present in the transformed cells is turned off. If this causes the cells to return to their normal state, then the transforming role of the gene can be established. Attempts in this direction are made by using conditionally lethal viral mutants of the virus, and the results available at the time of the Congress will be analyzed.

Another question is why the cells regularly contain a defective virus genome and why the defect always involves the synthesis of the viral coat. The answer may be that some viral functions and especially coat synthesis are incompatible with transformation. However, it is not clear why it should be so.

Studies with polyoma virus and SV40 have shown that these viruses induce the synthesis of cellular DNA and cellular enzymes under conditions of cytocidal infection. Induction occurs in cells in which, in the absence of infection, the normal synthetic processes are held in abeyance by regulatory mechanisms, due to cell crowding. Since transformation is also a release of cell multiplication from the same regulatory mechanism, it is possible that induction of cellular synthesis is one of the main mechanisms of cell transformation. At the present moment this is, however, a hypothesis without direct experimental support. Since the hypothesis is being tested experimentally a more precise evaluation may be possible at the time of the Congress.

Finally, the relationship of virus-induced transformation to spontaneous transformation will be briefly examined.

L 2

CANCER IMMUNOLOGY

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Tumor specific antigens capable of inducing rejection responses in genetically compatible (syngeneic) hosts and, in the cases where this could be tested, in the autochthonous, primary host as well, have been demonstrated in many experimental tumor systems, including both chemically and virally induced neoplasms. The immunological nature of the rejection reaction has been proved by different lines of independent evidence, such as the reduction of the threshold cell dose by preirradiation of the host, the increase in the threshold dose after preimmunization, the ability of lymph node cells or other immunologically competent cells from sensitized animals to damage specifically the target tumor cells and, in the case of lymphomas and leukemias, the appearance of humoral antibodies giving positive cytotoxic or fluorescence reactions. With carcinomas and sarcomas, humoral antibodies are less frequently demonstrated by these tests, but their presence can be often proved by other methods, such as e.g. immunological enhancement. Tumor specific antigenicity is now the rule rather than the exception for the experimental tumor systems investigated in this respect, even though there are considerable differences of detail with regard to antigenic strength and cross-reactivity patterns. One conspicuous exception is represented by those systems where tolerance prevails, due to the vertical transmission of a causative oncogenic virus to fetal or newborn animals. In such cases immunological reactivity may be entirely absent.

As a rule, chemically induced tumors are individually distinct with regard to antigenic specificity, even if induced by the same dose of the same chemical agent in the same animal genotype, and, in cases where multiple primary tumors have been tested, even if induced in the same individual animal. In contrast, neoplasms induced by the same virus show extensive and possibly complete antigenic cross reactivity. Both among chemically and virally induced neoplasms some etiological entities are characterized by weak and others by stronger antigenicity. Antigenic strength is also variable within an etiological group. A relationship has been found between the time of appearance of a given tumor during oncogenesis and its antigenic strength, with stronger antigenicity for tumors that appear after shorter latency periods.

A number of problems arise from these findings. The following questions will be discussed in particular:

1) What is known about the cellular localization, nature, occurence, and genetic determination mechanism of tumor specific transplantation antigens?

2) What host defense mechanisms are of importance for the rejection of antigenic tumor cells?

3) Why does rejection fail in the case of the "successful" tumors?

4) What is the significance of tumor specific transplantation antigens for studies on the etiology, prevention, and therapy of neoplasms?

L 3

CYTOGENETICAL ASPECTS OF CANCER: CHROMOSOME ANALYSIS IN THE STUDY OF NEOPLASMAS

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The hypothesis that chromosomal lesions have a fundamental relation with the neoplastic phenomena is not a new one. It has been proposed by Boveri in 1914 and later modified by Winge in 1930. The present discussion aims at an analysis of the thesis and confrontation of a logical model with the observed facts.

It is known that certain individuals with a constitutional anomaly of chromosomes are more liable to malignant processes than the normal subjects. For example, the infants with trisomy 21 suffer from acute leukemia 20 times more frequently than the normal. Similar tendency appears to exist in other types of trisomy 13 and 18.

Studies of karyotype of solid tumors have since long before demonstrated the frequency of aneuploidy, especially hyperploidy, but the major difficulty lies in the fact that the culture methods currently in use are more favorable to the normal cells than to the aneuploid. The idea of stem cell line is in expression of the fact that each tumor has a special karyotype from which different cells of each tumor present more or less conspicuous variation.

Classifications of chromosomal anomalies, according to the types of cancer, have been only infrequently attempted. The analysis of malignant proliferation of the bone-marrow-blood system has made an advance. Following the discovery of Nowell and Hungerford 1960, it has been known that chronic myeloid leukemia is associated with loss of a part of the long arm of one of the chromosomes of group G, perhaps 21. The constancy of that chromosomal lesion is remarkable in this disease. At the time of blastic transformation of chronic myeloid leukemia and during the course of acute myeloid leukemia, there are other known chromosomal changes, essentially in concern with the chromosomes group C and E.

In certain exceptional cases, it is possible (Lejeune et al. 1964) to observe an apparent affiliation of one karyotype to another. Consequently one may suppose that existence of such different chromosomal constitutions in the same tumor can be the evidence of progressive evolution of karyotypes from normal to pathological.

The above considerations will allow to imagine a model which, if confirmed by observation, can answer a fundamental question: Are the chromosomal anomalies the cause or the consequence of cancerization?

If it is supposed that the chromosomal changes have bearing on the behavior of the cells, it is logical to imagine that a given chromosomal lesion would be able to determine a characteristic cellular change. In the other words, one would observe in certain type of cancer, a particular chromosomal lesion which could be called the "common variant". The above example of deletion of one chromosome of group G in chronic myeloid leukemia is an illustration of this hypothesis. Two other cases of possible "common variant" have been noticed: in cancer of the ovary (Lejeune et Berger 1966) and in teratoma of the testis (Haines 1966).

Generalization of these observations remains as yet to be supported and they should be regarded as only indications at present.

From the cells with "common variant", a progressive (or sometimes regressive) evolution takes a start during which course chromosomal anomalies accumulate in the same cell line and reach the better fit combination. It is probable that a haphazardous redistribution of genetic factors borne by the chromosomes may be in compatible with the survival of the cells and a selection of certain effective combination will be done. The mechanism underlying the selection may be the existence of "forbidden combinations". Certain biochemical reactions (for example, successive stages of intermediary metabolism) must be dynamically balanced. Excess or absence of one enzyme, determined by excess or absence of one genetic factor, may disturb the balance and eventually induce death of the cell. As statistical analysis of very large number of karyotypes would allow to detect these "forbidden combinations", if they ever exist. It appears to be an important corollary today to give a positive verification to such combinations as retard the sensible metabolisms, if we shall put the biochemical markers of the chromosomes in concern.

In summary, if chromosomal hypothesis represents a part of reality, three fundamental points would be established: 1. Existence of "common variants", 2. Progressive clonal evolution, and 3. Selection by forbidden combination. Beyond a simple accumulation of morphological data the cytogenetics may thus become a real tool in cancer research.

(French abstract; see page 755)

L 4

SITE VARIATION OF ALIMENTARY TRACT CANCER IN MAN AND EXPERIMENTAL ANIMALS AS INDICATOR OF DIVERSE ETIOLOGY

Harold L. Stewart

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The information developed from the experimental induction of alimentary tract cancer in animals supports the assumption that the etiologies of cancer of the different segments of the alimentary tract in man are in all probability highly specific. Studies of geographic pathology indicate that cancer of different segments of the alimentary tract in man vary in frequency in different communities of the world. Specific regimens are now available for the induction of cancer of different segments of the alimentary tract in animals. Factors involved in these regimens are the chemical formula, physical state and metabolites of the carcinogens, the dose, the vehicle, the route of administration, the bacterial flora of the intestines and the strain, species and sex of the animal, and there may be others not yet recognized. The specificity for particular sites is well illustrated by some chemical carcinogens investigated. For example, N,N'-2,7-fluorenylenebisacetamide (2,7-FAA), benzidine and radioactive yttrium all induce adenocarcinoma of the large bowel in rats but only the 2,7-FAA induces this neoplasm in the small intestine and the glandular stomach as well. Almost all of the tumors induced by benzidine are limited to the rectum or rectosigmoid junction whereas the tumors induced by radioactive yttrium are distributed over the length of the colon. None of these three carcinogenic agents induce tumors of the esophagus but dihydrosafrol and N-nitrosopiperidine are both potent esophageal carcinogens. These and other examples of similar specificity from animal experimentation suggest that similar specific conditions operate in man to account for the striking geographic differences in the distribution of alimentary tract cancer.

The contrast between the frequency of cancer of particular sites in the alimentary tract in several geographic areas is illustrated by the following: (1) oral cancer - high in India and low in the United States; (2) esophageal cancer - high in the Transkei of South Africa, and low in Denmark; (3) gastric cancer - high in Japan, and low in the Transkei of South Africa; (4) colon cancer - high in the United States and low in Japan and (5) rectal cancer - high in Denmark and low in Mozambique. It is readily apparent from these observations and other similar observations that there is no general alimentary tract carcinogen affecting all population groups equally, and the elucidation of the etiologies of site specific cancer of the alimentary tract will require the combined efforts of the epidemiologist and experimentalist. The precise knowledge obtained from experiments with animals need to be extended and utilized in studies of cancer in man.

L 5