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BRITAIN'S MEDICAL RESEARCH COUNCIL'S
ANNUAL REPORT, APRIL 1971 - MARCH 1972

Arthur W. Frisch

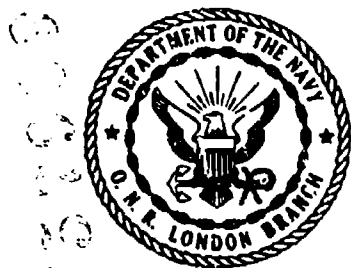
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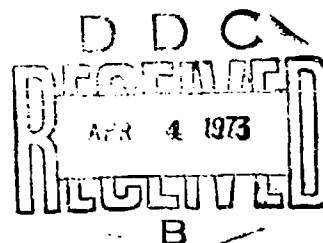
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BRITAIN'S MEDICAL RESEARCH COUNCIL'S ANNUAL
REPORT April 1971 - March 1972

By ARTHUR W. FRISCH

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BRITAIN'S MEDICAL RESEARCH COUNCIL'S ANNUAL REPORT

April 1971 - March 1972

INTRODUCTION

The Medical Research Council Annual Report, published by Her Majesty's Stationery Office, 49 High Holborn, London WC1V 6HB, is submitted each year to the Secretary of State for Education and Science. The details of all supported research are published in a separate Handbook for 1971-1972 which can be obtained from the Council's headquarters office, 20 Park Crescent, London W 1.

The Council consists of an Executive Committee of 13 members, a Secretary, three research boards and a Training Awards Committee. The following are included in the board representations: biological, tropical medicine, cancer and clinical research.

POLICY

The MRC section on policy reveals the thinking of the Council regarding the assignment of research priorities. Urgent problems are: arterial disease, including coronary thrombosis; drug misuse and dependence, particularly in relation to smoking and alcoholism; mental health and population control. Rapidly changing areas of research include cancer and environmental factors in disease and infections. Fields requiring more trained investigators are clinical neurology, clinical pharmacology, dentistry, dermatology, epidemiology, mycology, obstetrics and gynecology, and psychiatry. Grants in aid are being allocated to provide support for each of the research areas listed above. It is hoped that this brief summary will provide a quick overview of current research activities in biology and in medicine.

POLICY REVIEW

In 1966 the Medical Research Council initiated a program of reviewing selected areas of research for the purpose of achieving an increase in "the public's awareness of the Council's aims and achievements." Their list of the topics are given below and should be of interest to scientists in general, since it represents both productive and major problem areas in biology and medicine.

1966-67

Recent research on thrombosis
Ageing
Pulmonary hypersensitivity disease due to organic dusts
Some aspects of the organization of visual pathways

1967-68

Health hazards of asbestos dust
Bacterial sexuality and infectious drug-resistance
Chronic bronchitis
Recent studies on pulmonary ventilation
Use of rhesus monkeys in the study of mother-infant interaction
Brain hormone relationships
Chemotherapy of malaria

1968-69

Occupational health and toxicology
Epidemiology
Immunology
Molecular biology

1970-71

Epidemiology of cancer; a review of the work of the International
Agency for Research on Cancer
Hypertension; treatment of myocardial infarction
Air pollution
Mobility of the blind
Adenovirus structure
Neuromuscular disease
Suicide
Dental disease
Leprosy

1971-72 Reviews

The 1971-72 Reviews are discussed in detail below. They include the following:

Malignant disease: a review of recent research on therapy
Human cytogenetics
Tuberculosis
Inflammatory joint disease with particular reference to rheumatoid
arthritis
The neuroses
Anesthesia research
Dermatological research

The above reviews occupy approximately 50% of the content of the pamphlet which totals 141 pages. The material contained therein is summarized under various sub-headings with stress on current research being carried out, particularly in Britain. Also included are progress reports of research being conducted under MRC sponsorship.

A. Malignant Disease

The first review topic is titled "Malignant Disease: A Review of Some Advances in Treatment." The authors point out that the field of chemotherapy for malignancies has developed rapidly as a result of basic research, screening programs and cooperative studies of promising drugs in patients with unresponsive cancer. Present day management of malignancy includes a combination of surgery, radiotherapy and chemotherapy with encouraging results being reported for embryonal tumors of the kidney and the retina, seminomas and teratomas of the testes, acute leukemia in children and malignancies of the chorionic membrane. Particular advances have occurred in the management of Hodgkin's disease which is a slowly progressing, common malignancy of lymphoid tissues. Here, with combined radiation and drug treatment, the five-year survival rates have risen from 25 to 75%.

In Britain, as in the US, much effort is being devoted to a search for tests which will diagnose early malignancy. Progress is slow in this field despite some advances in cytology, mammography, soft-tissue radiography (xeroradiography), and despite attempts to demonstrate increased hormone levels or tumor antigens in blood and/or urine. In fact, the value of screening procedures for incipient cancer of the cervix is being reappraised in a large collaborative study in Cardiff.

MRC support of fundamental research has been allocated to the investigation of cell surfaces, transformation of cells by viruses, the study of chromosomal abnormalities, the biologic and biochemical properties of "T" (tumor) antigens, the poor immunogenic capacity of malignant cells, the role of "enhancing" antibody which protects tumor cells from attack by activated lymphocytes, clarification of the reverse transcriptase story, and an inquiry into the selective control of protein synthesis by ribosomes in a bacteriophage system.

In 1970 a Joint Coordinating Committee for Cancer Research was set up under the chairmanship of Lord Roseheim, KBE. Recommendations included collaboration with the recently organized United States program for screening chemotherapeutic drugs but not to the extent of duplicating US facilities. Other projects under consideration include a study of tumor specific antigens, "screening of environmental carcinogens, the possibility of using automated techniques for cervical cytology for early diagnosis and molecular biology related to cancer with particular reference to nucleic acid research."

The joint committee points out that plans for future studies must be on a "long term basis - that is, in terms of decades rather than years." It is, they said, "important for fundamental research to continue on a wide front, and for it to be carried out in close association with other biomedical research" and that "adequate training programmes for young scientists and career prospects should be provided." Finally, the committee recommended the establishment of oncological centers to provide opportunities for research and training at "all levels."

B. Progress in Human Cytogenetics

The easy identification of fluorescent banding patterns (acid Giemsa technique) represents an important breakthrough in chromosomal research. Answers to the following questions may now be forthcoming: (1) What is their structure and composition? (2) What is the meaning of individual variations in size, shape, number, etc.? (3) Can small structural changes be detected and correlated with disease? (4) How long before there is a detailed map of human gene linkage?

An important technical advance made in Britain is the development of a computer-controlled microscope which selects dividing cells for projection on a television screen. Thus a "composite karyotype" is obtained by the computer from a "series of cells." These technical advances will allow for the mass examination of selected populations looking for chromosomal deviations and for environmental mutagens.

C. Dermatology

The third short review is titled "Dermatological Research" with acne as the presenting topic. The pathogenesis, including the increased activity of the sebaceous glands, the obstruction of the duct by cornification, the production of unsaturated fatty acids by bacteria and treatment with tetracycline are briefly discussed. An interesting tissue culture technique for studying skin is presented in which radioactive carbon is incorporated into the sebum. The excretion products and the gland contents are analyzed after a period of culture. The sebaceous glands from patients with acne contain more wax esters and the secretion is, therefore, viscous enough to block the duct.

Photosensitivity problems are being investigated with the aid of the monochromator which produces a light beam of a single wavelength. Immunofluorescence and electron microscopic techniques are being broadly applied in Britain as in the US. The latter is of particular value in patients with excessive cornification of the palms and soles (tylosis) who show persistence of intracellular cement. This is removed by the application of trypsin with notably successful results.

The review is concluded with the following paragraph. "The Council's Unit for Research on Experimental Pathology of the Skin (Director: Dr. C.N.D. Cruickshank) has been active in promoting a scientific approach to dermatology since its formation and, through grants to university staff and individual clinicians, the Council is supporting a wide variety of studies of the skin and its diseases in which biochemical, pharmacological, physical and immunological techniques are being used."

D. Arthritis

The fourth review deals with "Research on Inflammatory Joint Disease with Particular Reference to Rheumatoid Arthritis." This discussion is

largely theoretical and deals with inflammation, rheumatoid factor, complement, autoimmunity, infection, formation of immune complexes and deficits in the ability to distinguish self from non-self.

E. Neuroses

The topic for the fifth review is titled "The Neuroses" and defines the neurotic individual as one who may "develop symptoms under an amount of stress which would not affect other people." An important task is to devise a test which will detect potential neurotics. Research toward this objective is being conducted in the MRC Unit of Epidemiological Studies in Psychiatry (Director, Dr. N.B. Kreitman). This group is also investigating families. Thus "if one partner in a marriage suffers from a neurotic disorder there is greater than chance expectation that the spouse will do so too." About half the wives of neurotics manifest symptoms, but "there is no evidence to suggest that neurotics mutually select each other as marriage partners." Therefore, it would seem that the reactions of one member of a family is strongly influencing the other. In a study of university students it was found that one in four had emotional difficulties the first year and that the symptoms, whenever they occurred, were associated with "poor academic performance."

A new form of treatment for neurotics is termed "Behavior Therapy, desensitization treatment." It consists of an attempt to gradually induce anxiety in the patient by real or imagined situations and then "neutralizing" the state by means of "relaxation techniques." Desensitization has been shown to be most helpful in certain specific, acute anxieties where only a single factor operates. The "flooding treatment" also new, is one in which increasing anxiety is produced and the "patients are encouraged, with the support of the medical and nursing staff." This treatment may be particularly effective in subjects with phobias.

F. Anesthesia

The sixth article is a "Preview of Progress in Anesthesia Research." Much of this short summary centers around MRC supported projects and the progress made to date. Thus the Division of Anaesthesia of the Clinical Research Centre (Dr. J.F. Nunn, Head) have shown that the proteins of the mitotic spindle are altered during anesthesia. Cerebral blood flow, according to Prof. D.G. McDowall and his colleagues at Leeds, is "greatly increased" by volatile anesthetics. Dr. B. Delisle Burns of the National Institute for Medical Research has attributed automatic respiratory movements to "two types of neurones in the medulla oblongata. One group of cells controls inspiration and the other controls expiration providing a 'bi-stable' system in contrast to the unstable concept which postulated inhibition of a set of inspiratory cells." A barbiturate, sodium thiopentone, was used to work out the bi-stable mechanism in the cat.

Other reported briefs include an on-line computer study of physiologic changes during surgery, and neurophysiological experiments to support the

"gate control theory" of pain which assumes there is a "convergence and interaction" in the brain of "different types of impulses at a 'gate,' the setting of which is influenced by controls descending 'from the brain.'"

G. Tuberculosis

The last review, "Progress in the Chemotherapy of Tuberculosis," begins with the statement that there are 11,000 new cases per annum in England and Wales, a leveling off of the previously declining slope of the curve. The Council is attempting to shorten and simplify anti-tuberculosis chemotherapy "with the aims of making it less toxic, more effective and more foolproof." To this end, studies are in progress in Madras and in East Africa (1) to measure the results of a six-month instead of an 18-month regimen and (2) to determine the value of bi-weekly or weekly (rather than daily) drug administration, a program which allows for more supervision. Some "laboratory evidence" has been obtained that rifampicin and ethambutol may be more effective if given intermittently in high doses than in small, daily doses. However, reactions to rifampicin have been noted in a few of the patients. A byproduct of the development of better drugs and regimens for the management of tuberculosis is evident from calculations by the British Office of Health Economics. Thus in 1968, as compared with 1954, approximately \$75 million was saved in sanatorium fees; 150 million in savings was obtained from increased productivity, and another 50 million in sickness benefits, an overall total of \$275 million. This is just one example, among many, where scientists have returned to society much more than was expended in the original funding of the project.

PROGRESS REPORTS

Interdispersed among the reviews are selected progress reports concerning MRC supported projects in various fields. The first, titled "Genetics: Reports of Some Recent Work," begins with a section on familial hypercholesterolemia which is characterized by an elevated beta-lipoprotein level in the plasma. If the disease is homozygous (both parents contribute), patients frequently develop extreme hypercholesterolemia, associated with evidence of heart disease in childhood and usually expire before age 20. About one in every 250 individuals in Britain carries a double dose of the mutant gene. The relationship of the hyperlipidemia to coronary artery disease is discussed.

The MRC Cell Mutation Unit under Dr. B.A. Bridges has developed a procedure for inducing mutations in cultured hamster cells and also in bacteria using varying doses of chemical mutagens, thus allowing for "rapid screening of chemicals" for this property.

The section on Cell and Molecular Biology describes a particularly fascinating project being carried out by Dr. Richard Gardner of Cambridge University who incorporated three to five embryonal mouse cells into an 80-cell

embryo and was able to demonstrate by chromosomal studies that "all the tissues and organs examined proved to be complex mixtures of cells of the two types." The data demonstrate the totipotential nature of the donor cells and their ability to mix within the embryo and still provide functioning organs.

The same section also comments on studies in progress at the Beatson Institute for Cancer Research under the direction of Dr. John Paul. This group is attempting to gain insight into the process whereby genes are controlled. An elegant technique has been developed for recognizing a precursor of mouse messenger RNA which, when introduced into a de-nucleated frog's egg "takes over the frog cell's synthetic apparatus" and forces it to make mouse hemoglobin.

Studies in the Genetics Division of the National Institute for Medical Research under Dr. R. Holliday are concerned with cellular aging in fungi and its association with the formation of defective protein. The data support the theory that "with time, cells might gradually lose their capacity to synthesize proteins accurately and that this trend, once started, would be irreversible." In recent studies with human fibroblast cultures, the Holliday group have demonstrated that the heat lability (60° C) of glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase increase with senescence of the cells. Similar changes can also be obtained using 5-fluorouracil in young fibroblasts.

Work on the long term retention of strontium in tissues is continuing at the Chemistry Section of the MRC Radiobiology Unit formerly under the direction of Dr. C.E. Harrison (retired). They have obtained a compound from seaweed which, when fed to animals, prevents the gastrointestinal absorption of strontium without affecting the calcium uptake. The practical applications of this discovery to strontium storage in man and in animals are obvious.

The Division of Cell Pathology in the Clinical Research Centre under Dr. A.C. Allison has been studying the function of the filamentous, contractile, proteins which are found just beneath the limiting membrane of mammalian cells. This particular system, unlike the one in striated muscle, appears to be selectively paralyzed by a fungal derivative called Cytochalasin. The associated cell functions which are affected include the loss of phagocytic ability to leucocytes, inability of basophilic cells to degranulate and to liberate histamine and other vasocative compounds, and inability of cells to release their hormone-containing granules. Other cell movements such as the formation of mitotic spindles and the release of immunoglobulins do not appear to be affected.

The molecular changes during muscle contraction are under investigation by the Muscle Biophysics Unit (Director: Prof. Jean Hanson FRS) and the Laboratory of Molecular Biology (Head of Subdivision: Dr. H.E. Huxley FRS), using X-ray diffraction and electronmicroscopic methods. Of particular

significance is the discovery of a "new protein that is located together with myosin in the thick filament" which suggests "the existence in that filament of a control mechanism similar in principle to the one in the thin filament."

The MRC Cellular Immunology Unit (Director: Prof. J.L. Gowans FRS) has utilized the technique of passive transfer of lymphocytes to demonstrate that they do respond selectively to antigen. Transfused and radioactively labeled lymphocytes are recovered from thoracic duct lymph and can react specifically (graft rejection procedure) with heterologous but not with homologous tissue antigen.

Studies of bone marrow (B) and thymus (T) derived lymphocytes and their interaction are being continued at the National Institute for Medical Research (Immunology Section: Dr. J.H. Humphrey FRS). Current theory maintains that the "different functions of T-cells, as helpers of B-cells and as killers of foreign cells, are seen as manifestations of the same fundamental process of immune surveillance." Thus when B cells bind to "foreign" cell surfaces the complex is recognizable by T cells which attach and destroy the unwanted cells and, at the same time, stimulate the antibody containing B cells to replicate.

Other immunologic projects include a study of purified lymphocyte glycoproteins containing receptors for mitogens, the research of Prof. M.A. Epstein (Chemical Research Centre, Division of Immunology) on the "distribution and behavior of the immunoglobulin molecules of the lymphocyte surface membrane that act as antigen-specific receptors," and stimulate the "killer" macrophages in contact hypersensitivity.

Recent work by Dr. H.G. Pereira (Head, Virology Division, National Institute for Medical Research) has shown that genetic recombination occurs readily between influenza viruses of human and animal origin and that the new variants manifest properties of both parents. These experiments may serve to explain the antigenic complexity of the families of these viruses. The technique of genetic recombination has also been used by Dr. D.A.J. Tyrrell FRS (Clinical Research Centre, MRC Common Cold Unit) to develop an attenuated stable influenza variant which protects against A2 infection without producing significant symptoms. The Common Cold Unit has been investigating an amantidine derivative which reduces the occurrence and symptomatology of influenza infection in volunteers without "detectable side-effects." Two additional areas of virology under investigation include (1) a study in volunteers of an agent related to the picornaviruses (polio and entero-groups) which produces symptoms of non-bacterial gastroenteritis and (2) a continuing study of the tumorigenic and interferon-inducing properties of variants of adenovirus type V. As a result, a new technique has been developed for recognizing transformation of infected rat embryo cells, and two groups of mutants have been obtained which no longer stimulate interferon synthesis.

In Hematology interest is focused on an abnormal hemoglobin from Thailand called TAK which differs from other variants in that it contains 10 extra amino acid residues on one end of the beta chain (Prof. H. Lehmann FRS). Possible ways in which such a variant could originate are discussed.

At the Dunn Nutritional Laboratory in Cambridge Dr. E.H. Kodicek is continuing his work on 1,25-dihydroxycalciferol which is believed to be the "active form of vitamin D in target tissues" and is particularly concentrated in the nuclei of intestinal cells, in bone and in the kidney where it is converted to 25-hydroxycholecalciferol by an enzyme in the mitochondria. Currently attempts are being made to prepare synthetic 1,25-DHCC for clinical trial. The Dunn Nutritional Laboratory is also investigating the "clinical structure and metabolic fate of the bound nicotinic acid of cereals (niacytin)" and its absorption from the intestine in normal and nicotinic-acid-deficient rats. In nicotinic-acid-deficient rats more of the biologically inactive vitamin is absorbed, presumably because of the increased permeability of the deficient intestinal mucosa to undigested macromolecules.

In the field of Social Medicine the MRC Unit on Environmental Factors in Mental and Physical Illness (Director: J.W.B. Douglas) find that one in ten persons who leave school at age 15 have serious problems in "settling at work." Those who followed the advice of the Youth Employment Service did considerably better. For the past ten years the MRC Social Medicine Unit has been studying children from one London borough who have had experience with the juvenile courts. "Of the three main influences in a child's environment - neighborhood, school and family - the first two (neighborhood, and school) have been shown to be more important in determining whether a boy becomes delinquent at all." It is recognized, of course, that the family role is also important, but this unexpected finding will need to be developed further.

The emotional impact of an abortion has always been surmised but never really investigated. Therefore, the MRC Medical Sociology Unit (Honorary Director: Prof. R. Illsey) of Aberdeen has been looking at the effects of abortion in association with gynecologists and psychiatrists. Of 167 women interviewed before and again five months afterward "almost all (83%) had no subsequent doubts that the decision had been right." A total of eight women, four married and four single, expressed regrets. Twelve had doubts prior to the operation but were happy about their decision afterward and only one felt that she had made a wrong decision. On the reverse side, the majority of those who refused an abortion were also satisfied with their decision to continue the pregnancy, although some subsequently put up their babies for adoption; a longer follow-up is in progress.

I was interested to learn that deaths from heart disease and stroke are related to the nature of our drinking water. Thus "the softer the water the higher the mortality rates" and conversely "hardness of the drinking water appears to protect against cardiovascular disease."

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Furthermore, in studies of towns where water supplies have been changed from hard to soft or vice versa a corresponding change in cardiovascular mortality has also occurred. The MRC Social Medicine Unit in collaboration with St. George's Hospital are examining this phenomenon by doing clinical, biochemical and postmortem studies on men in six UK towns with hard waters and six with soft. To date they find unusually high levels of heart disease in some towns with soft water. The cardiovascular mortality appears to be inversely related to the calcium content of the water and not to the magnesium. The mechanism is, as yet, unknown.