Human Ecology (E. Sunderland). An attempt was made to examine the adaptability of the people of Shishan and Druz and ultimately the Bedouin to the dry, hot desert environment. The first step was to obtain a measure of the heterogeneity of each community in terms of colour blindness, fingerprinting, height/weight ratios, skin colour and blood grouping.

The pedigrees of thirty-two families in Shishan and eighty-three in Druz were recorded. The bloods were grouped for the antigens A, B and O, C, c, D, E, e, M, N, S, s, K, k, P and Fy^a. These analyses together with examinations of blood smears for sickle cells were done at the Anthropological Blood-Grouping Laboratory in Beirut. Azraq Shishan contains 229 people living in thirty-eight households and Azraq Druz contains some 1,075 individuals in about 120 households. The data obtained serve to establish some basic genetic "quantities" for the Azraq villagers, but far more work along these and other medico-genetic and social lines could be and should be conducted here.

Follow-up. On the basis of this preliminary report the expedition has made its recommendations in a project paper for an International Biological Station at Azraq to the CT Sectional Committee. In this article the potentialities for future biological research at Azraq are described under the various disciplines together with a section on the constitution and finance of the station.

[1] Mountfort, G., *Portrait of a Desert* (Collins, London, 1965).
[2] Boyd, J. M., *Nuffield Travelling Fellowship Report* (Nature Conservancy, London, 1965).
[3] Jaeger, J., jun., *Report to USAID Jordan* (Amman, 1965).
[4] Hemsley, J. H., and George, M., *Azraq Desert National Park, Jordan; Draft Management Plan* (Nature Conservancy, London, 1966).
Ferguson-Lees, I. J., "Wryneck's Rapid Journey after Off-passage Recuperation", *Bird Study* (September, 1966).

CANCER RESEARCH

The 700-page 43rd Annual Report of the British Empire Cancer Campaign for Research for 1965 describes the investigations financed by the Campaign or carried on at institutions working in association with it. The subject matter of the book can be divided into three parts which are dealt with separately in what follows.

Carcinogenesis and the Biology of Cancer Generally

THOSE who are engaged in some different field, and even some who are in cancer research, may not perhaps appreciate that the work of Doll and Hill (1950) on the relationship between cigarette smoking and lung cancer, and that of Gross (1951) in the United States on mouse leukaemia virus, represent the outstanding achievements of the past 16 years. These two themes—environmental factors and virus—and also immunology, malignant transformation *in vitro* and experimental carcinogenesis are the most interesting features of cancer research today. The report of the British Empire Cancer Campaign contains numerous references to DNA, but this lies on the sidelines and in more academic spheres. Among the accounts which it contains of the hundreds of investigations on all aspects of cancer research, some are highly condensed, and others read more like laboratory note-books, as though some kind of justification of grants is required.

The reader embarking on the report proper can find a little light relief from, first, an example of the intimidating technicalities used by scientists when they write about their special branches of research. Thus Hambly, at Cambridge: "Relation of Linkage Group VII to Lung Tumour Susceptibility in the Mouse. A six generation breeding programme is under way to reconstitute the linkage Group VII chromosome wavy-2, tumour susceptibility and vestigial tail, using a stock of $wa_2+^{Tm}vt/+^{wa2}Tm+^{vt}$ isogenic with strain A/Cam. This has reached the third generation. It should yield, during the first half of 1966, some useful data on the relationships between tumour susceptibility and the markers wa_2 and vt". Second, there is a fine example of scientific ultra-caution: Green at Leeds commenting on his interpretation of carcinogenesis as the result of immune reaction writes, "One of the factors which might contribute to the overall activity of a carcinogen is the ability to suppress the host's immune defences (Berenbaum, 1964). The results of a small experiment by Mr. Westrop tended to support this view but, in keeping with most of the attempts which have sought to evaluate the role of the immunological mechanism in carcinogenesis, it hints that many variables, such as sex and age of the animals and the scheme of carcinogen treatment, have a decisive influence on the final observations especially if the latter are of the all-or-none variety", and "Whatever the exact interpretation of the results is, it would seem that the rat subcutaneous tissues may have been sensitized by the oral dose of DMBA. An explanation in terms of immune processes seems most likely, though one cannot exclude a summation of the orally ingested compound and that given remotely. This latter explanation, however, does not seem likely". Third, there are some airy pronouncements by Burch of Leeds in his theoretical treatment of the problem of carcinogenesis: " . . . spontaneous and induced gene mutation leading to disturbed-tolerance auto-immune and malignant disease in mammals probably entails not point-type mutation (such as base transition, transversion or deletion) but a switch in messenger RNA transcription from the regular strand of DNA . . . over to the base-paired complementary anti-parallel strand of the same structural gene (Burch and Burwell, 1965). This theory is capable of solving the long-standing paradox concerning the cross-section of mammalian genes for radiogenic mutation. The mutagenic event probably blocks messenger RNA transcription from the normal strand of DNA, removes a DNA-strand-determining polypeptide chain from the minor groove of the double helix, and thus allows transcription to occur from the anti-parallel strand of DNA".

At the Middlesex Hospital the study continues, by tissue culture and electron microscopy, of Burkitt's lymphoma found in young negroes in Uganda. The tumour is probably caused by a virus which may either be specific to it or carried preferentially as an unknown passenger; passage to monkeys results in cystic bone changes and the appearance of sheets of lymphoblastic tumour cells. (See also the reference to Burkitt in the third section of this review.)

Alexander and his colleagues are working on the treatment of animal tumours by immunological methods, and find that tumour inhibition can be achieved in transplantable sarcoma in rats induced by benzpyrene if they are injected with lymphocytes from rats which have been immunized with the same tumour material; the lymphocytes must act indirectly, for radioactive labelling shows that they collect in the spleen and not in the tumour undergoing treatment. The lymphocytes from the immunized rats can be replaced by lymphocytes from immune sheep provided that massive doses (10^9) of cells are used and immune horse lymphocytes are also effective; it is concluded that anti-tumour action relies on the specific antigens which are individual to each tumour.

Davidson and colleagues at King's College Hospital are using tissue cultures of lymphocytes to investigate the effects of anti-leukaemic drugs and, at the same centre, Tee and Wang are continuing their experiments with tumour-specific antigens; six serologically different normal tissue antigens and nine serologically different tumour antigens have been identified using heterologous antisera and the double diffusion technique on 92 human tumours and 80 normal tissues. No clear-cut correlation has been found between the presence of tumour antigens and the degree of malignancy; loss of normal tissue antigens was observed in 15 out of 19 tumours for which autologous normal tissues were available. "The immune 7*S* γ-globulin produced in mice against homologous transplantable tumours has a greater molecular heterogeneity than normal 7*S* γ-globulin from the same strain. Immune 7*S* γ-globulin produced in this way also had a significantly longer biological half life than normal γ-globulin when labelled with ^{131}I and introduced into normal mice".

Salaman and collaborators are continuing their work on MSV (mouse sarcoma virus) . . . "the method of titrating MSV which gives the highest sensitivity is that used for Moloney and other leukaemogenic viruses, namely, the intraperitoneal injection of serial dilutions into newborn mice". But there is hardly any reference to carcinogenesis by these viruses—the experiments are concerned almost wholly with the virology of the carcinogenic viruses and deal almost entirely with the physical properties of the virus (sensitivity to ether; centrifugation; storage; particle size; neutralization by antisera; electron microscopy and effect of virus on the immune reaction of mice). Using the Friend virus and a related virus-RV (Riley's plasma lactate dehydrogenase elevating virus) Salaman also describes the production of splenomegaly and cytotoxic antibodies. Referring to the urethane leukaemia virus he says: "This agent derived from urethane-induced leukaemia in mice (Salaman and Flocks, 1964) has given rise to several variants, one of which resembles Friend and Rauscher viruses in its pathological effects". (The extraordinary fact of a carcinogen creating a virus is, incredible as it may read, passed over without comment.)

Harris and Schild at Sheffield have been cultivating *in vitro* cell lines derived from hamster tumours induced with adenovirus type 12; immunization against the tumour transplanted *in vivo* by tissue cultured cells can be achieved with vaccines of adenovirus 5 and 12, but neither 18 nor other members of a large series of adenovirus types are effective. Adenovirus types 3 and 7 will proliferate in hamster tumour cells but not in normal diploid cells.

At the Mount Vernon Hospital, Powell is pursuing his study of the effect of carcinogens on *in vitro* cultures of normal cells; the account of this work is lengthy, but nowhere mentions tests of malignant conversion by growth *in vivo*; he relies on cytological criteria and refers to a "a cytologically malignant transformation in monocytes, fibrocytes and epithelial cells derived from rat and mouse embryo lung, skin and muscle tissues cultivated *in vitro*".

At St. George's Hospital, Martin *et al.* have examined abnormal proteins in myelomatosis and associated neoplasms, and at the Westminster, human neoplasms are being cultured in the cheek pouch of hamsters in order to observe microvascular responses to homografts of normal hamster tissues and heterografts of normal and malignant human tissue; a similar technique is in use at the Great Ormond Street Hospital with neoplasms of children.

At the University of Bristol, Sparshott and Meek have carried out experiments on the pattern of distribution of DNA in cell cultures; they conclude that many cell lines may behave as neoplastic tissue on implantation *in vivo*, and that the gross karyotypic variation so common in cultures of malignant and normal cells is not an essential feature of malignant transformation *in vitro*.

Baldwin and collaborators at Nottingham reporting on their investigation of tumour immunology state "Tumour specific antigens capable of evoking at least some degree of resistance towards tumour grafts in isogenic or even autochthonous hosts have been demonstrated in carcinogen-induced tumours in mice and to a lesser degree in rats". Baldwin describes experiments in which antigens to liver tumours induced in rats with dimethylaminoazobenzene (DMAB) could confer immunity to challenge with 10^5 live cells, but this resistance broke down at 10^6 cells; he concludes "available evidence suggests that the tumour-specific antigens are highly labile, inactivation rapidly following cell rupture". " . . . Peritoneal cells from immune rats prevented growth of the tumour used for immunization, but were completely ineffective against a second DMAB-induced liver tumour. These observations further support the view that DMAB-induced liver tumours possess individual specific antigenicities."

No appreciable activity of any tumour antigens could be detected in rat mammary adenocarcinomata induced by treatment with 2-acetylaminofluorene, or in a "spontaneous" rat reticulum cell sarcoma, or in a spontaneous squamous cell carcinoma, when the tumours were first killed by irradiation before injection as immunizer, but some protection was given when the tumours were killed by ligating their blood supply.

Orr at Birmingham has continued his researches on breast tumours produced in mice by painting the skin with carcinogens. When he painted three different strains of mice with dibenzanthracene he found that lactation completely inhibited mammary cancer in the *IF* × *C57* strain hybrids, and that *C57* virgins also did not develop tumours; but in the *IF* strain—in virgins (isolated or grouped), in pseudopregnants, in forced breeders, and in lactating breeders—the incidence of mammary tumours was as high as 56–100 per cent.

The report from the Leeds centre states that in experiments in chemical carcinogenesis in tissue culture the action of the carcinogen " . . . is complicated by [the] tendency [of the cells *in vitro*] to show 'spontaneous' transformation to a form which produces malignant tumours on re-implantation into compatible animals". "Complicated" is scarcely the *mot juste* in this connexion; spontaneous malignant transformation *in vitro* is one of the most interesting phenomena ever observed in cancer research, and it is deplorable that the great majority of cancer research workers neglect it.

In Uganda Burkitt has elaborated on his original study of lymphoma by investigating the influence of altitude and finds that the tumour is rare in the heavily populated south-western region of Uganda; other types of lymphoma appear to be entirely independent of altitude and are closely related to the population density of the area. From the same centre (Kampala) Fripp reports that bladder cancer in the community of Bukoba seems to be due to the use of plantain as a food; this plant contains a bladder carcinogen—3-hydroxy anthranilic acid. Hansen finds that the urinary excretion of the acid is between five and ten times higher in plantain (matoke) eaters than in East Africans from regions where plantain is not part of the staple food. At the laboratories in Bulawayo statistical survey of cancer by site in native and white populations shows that liver is still the most common site in Africans and the skin (45 per cent) in whites.

The C.S.I. Hospital in South India reports that oral cancers alone account for 74 per cent of all cancers.

The National Cancer Institute of Canada is supporting a comprehensive scheme of cancer research at a number of laboratories; the subjects of investigation represent very typical examples of work carried on elsewhere; in all, more than 130 studies are mentioned by title. At the New Zealand branch in Otago work proceeds on a particularly sensitive strain of mice—the *NZO*; of a series given 1 mg urethane per g body weight when 5–7 weeks old, the majority developed large numbers of papillomata, haeman-

giomata were seen in most and lung adenomata in all the mice; 2-aminofluorene caused thyomata. The closely related *NZB* strain did not react at all to urethane injection, and no papillomata were found. At the Australian centres in Adelaide and Sydney much the same type of cancer research is being done as in laboratories the world over, such as dosimetry, isotopes and calibration in radiation; carcinogens, chemotherapy, DNA, RNA, steroids in cancer; chromosomes in tumours and other tissues, tissue culture of malignant and normal cells, viruses, morphology and cytochemistry of neoplastic cells, environmental characteristics of cancer incidence.

Stoker in Glasgow has found that two types of response are elicited by polyoma virus acting on susceptible cells *in vitro*; in one shown by mouse embryo cells, the virus induces cell lysis with the production of large amounts of progeny virus, and in the second (a continuous line of hamster kidney fibroblasts) a small proportion of the cells are transformed by the virus infection and become malignant.

The report from the Glasgow Veterinary School is on lymphosarcoma in domestic animals—a virus has been grown in tissue culture from a lymph node of a feline lymphosarcoma. I. HIEGER

Radiobiology and Radiotherapeutics

In the past two years radiobiology has made exceptional progress, and work supported by the Campaign has contributed in no small measure. The radiosensitivity of cells is influenced by many factors, both extrinsic and intrinsic; more of these are being identified and knowledge is being gained about some of the biochemical mechanisms responsible. Until recently, much of this work was done with cancer cells and these continue to provide valuable leads; exceptionally resistant cell lines have been isolated from growing culture (St. Bartholomew's Hospital) as well as from a spontaneous carcinoma (Mount Vernon); HeLa cells were shown to be capable of withstanding very large doses if cooled to $-196°$ C. The determining factor in radiotherapeutic procedures is not, in general, the response of the tumour, but the dose which the normal tissue can tolerate. There is now an urgent need to learn more about the response of normal cells and organs to irradiation.

At the London Hospital the functional state of the thyroid of the rat was shown to have an effect on its radiosensitivity. Growth, stimulated by a goitrogen, was halved by irradiation with 750 r. The X-ray sensitivity was decreased if, at the time of irradiation, thyroid function was depressed by TSH. At Mount Vernon Hospital techniques have been developed to measure quantitatively the *in vivo* radiosensitivity of epithelial cells of mouse skin, which was found to fluctuate depending on previous exposure. Dividing cells in regenerating liver were about three times as resistant as those of skin. The sensitivity of mouse oocytes was shown to depend critically on the stage of maturation and there is an intermediate stage of high radioresistance (St. Bartholomew's Hospital). Paradoxical oxygen effects, such as protection by anoxia, have also been observed in the mouse ovary. Extensive investigations of the effects of X-rays on growing bone are reported from Guy's Hospital and on cells in the developing retina from the Strangeways Laboratory. The response of the central nervous system is particularly interesting and seems to be much more marked in hypertensive than in normal rats (St. Mary's Hospital). Relatively small doses to the brain produce no detectable effects alone, but greatly reduce the capacity of subsequently induced surgical lesions to heal. Also at St. Mary's Hospital it was shown that cysteamine is capable of providing good protection to animals even in the most severe hypoxia.

Studies with micro-organisms most clearly indicate the role of the physiological state in determining radiosensitivity. The increase in sensitivity of spores after plating on agar was shown to be an effect of altered metabolism and not to uptake of water (Christie Hospital). The well known protective action of sulphydryl compounds suggested that there might be a correlation between the sulphydryl content of cells grown under different conditions and their radiation response; but none was found (Mount Vernon). The increase in radioresistance of cells of *E. coli B/r* on passing from the logarithmic to the stationary phase of growth was shown to be prevented by the addition of sulphanilamide (Chester Beatty Research Institute) because repair of a radiation lesion was prevented. Repair was also evoked as an explanation for the fact that the dose-response curve of *Serratia marcescens* to X-rays was not exponential with dose, but was a continuously curving function indicating that the probability of killing increases with dose (Mount Vernon).

Biochemical investigations at the Chester Beatty Research Institute led to the concept that a key factor in radiosensitivity is the capacity of the cell to restitute radiochemical damage sustained by the DNA. The complex enzymatic repair process is itself radiosensitive and no simple relationship between initial damage (that is, dose delivered) and cell death is therefore possible. Using the very radioresistant organism *Micrococcus radiodurans*, restoration of breaks in the main DNA chain induced by radiation were measured directly. The action of an exonuclease seems to be necessary before rejoining can occur and the enzyme involved may be isolated soon.

When fractionated doses are given, as in conventional radiotherapy, sub-lethal damage is important, that is, the first dose does not kill but makes the cells more susceptible to a second dose. It has been known for some years that mammalian cells can recover from this type of sub-lethal damage and the rate of recovery plays a part in determining the total effect of a fractionated course of radiation treatment. There are many other factors, however, including blood vessel damage, cell migration and vasodilation. Indeed, the sparing effect seen after fractionation due to sub-lethal recovery can be entirely reversed by physio-pathological factors (St. Bartholomew's Hospital). Because the first dose of radiation is likely to alter some of the many factors which influence radiosensitivity at the cellular level, radiobiology cannot at present substitute a scientific basis for the *ad hoc* approach of determining fractionation which is, as yet, all that is available to the radiotherapist. Work with experimental tumours, particularly primary tumours, however, has indicated variables that are likely to be particularly important. The response and adjustment to continuous irradiation of organs *in vivo* and of cell cultures *in vitro* is throwing much light on the complex interplay of factors involved in fractionation such as intracellular recovery, cell replacement, stem cell selection and changes in anatomical structure. Further progress in this difficult field is reported from the Biophysics Department of the Institute of Cancer Research. Related studies are being carried out at the Christie Hospital where, in addition to experimental projects, extra-corporeal irradiation of the blood of leukaemia patients is being tried.

It is impossible to do more than mention the very extensive body of work in the field of radiation chemistry. The new technique of pulse radiolysis pioneered at Mount Vernon and the Christie Hospital and now also taken up at St. Bartholomew's Hospital is providing detailed kinetics of the rate of reaction of many substances with the radicals produced by radiation in water. The nature and life-time of some intermediary radicals produced in such reactions have been identified and these studies have led to hypotheses of the mechanism of action of some well known radio sensitizing agents such as iodoacetamide. The nature and role of hydrogen atoms in these reactions have been difficult to disentangle from the reactions of other