(3) In the session dealing with the inheritance of cancer in man, the symposium was presented with a general survey of the problem by Prof. T. Kemp (Copenhagen). The investigations carried out in Denmark suggest a genetical basis for predisposition to cancer, involving several genes, and furthermore that the localization, pathological features, rate of development and the time of onset of tumours may be similarly controlled. Since environmental factors also play a part in the development of particular kinds of cancer, any analysis of the heredity of cancer in man inevitably meets great difficulties. In order to compare the incidence of cancer in families with that in the total population, a critical collection of control material is required, and the difficulty of obtaining such material was stressed by several participants in the symposium. To a certain degree the problem has been solved by Prof. L. S. Penrose (London) and his collaborators, using the Registrar-General's statistics for calculating the expected proportion of breast cancer and cancer deaths among relatives dying at all ages and at most periods of the immediate past: the expected death- and incidence-rates for relatives can thus be compared with the observed figures. Prof. Penrose analysed the family-histories of 510 cases of mammary cancer by this method and found that the proportion of deaths due to mammary cancer in the patients' relatives was significantly increased, the rates for other types of malignancy remaining unchanged. Similar conclusions were arrived at by Prof. D. Smithers (London) from the study of family-histories of 459 patients with cancer of the breast. Prof. Penrose concluded that a specific genetical agent is responsible for mammary cancer in man. Evidence concerning the nature of this agent was obtained from studying incidence in paternal and maternal relatives, laterality, age of onset and history of breast feeding in the patient's own infancy, from which Prof. Penrose found some indication that the specific agent might be cytoplasmic but probably not transmitted through the milk.

The studies carried out by the Danish Cancer Registry on twins, under the direction of J. Clemmesen, were presented by Dr. Th. Busk (Copenhagen). From these it seems there is a greater tendency to higher incidence of cancer among partners of identical twins afflicted with cancer than among partners of fraternal twins with cancer, and also a clear tendency for tumours in identical pairs to affect corresponding organs in both partners, whereas this is not the case among fraternal twins. Though the investigation covered about 30,000 cancer patients, only 187 twins with cancer were found suitable for analysis.

It is hoped that the investigations reported at the symposium will direct attention to the importance of recording comprehensive family histories. The need for collaboration in these matters between physicians, geneticists and statisticians was illustrated in a paper by Dr. P. C. Koller (London), who presented two family-histories of xeroderma pigmentosum, one showing an unusually mild manifestation of the disease. The distribution of this condition among the two sexes and the unusual pathological features throw further light on its genetical basis and suggest that we may need to modify Haldane's concept of partial sex-linkage in respect of this particular disease.

The proceedings of the symposium will later be published in the *British Journal of Cancer*.

P. C. KOLLER

THE *Rh* FACTOR OF BLOOD

DURING the summer meeting of the British Medical Association in Cambridge, the pathological section held a discussion on "Recent Advances in our Knowledge of the *Rh* Factor". Only the opening speaker kept strictly to this title, the other two invited speakers reading papers on closely related topics; therefore each contribution will be described separately.

Prof. D. F. Cappell, of Glasgow, first briefly described the history of the discovery of the *Rh* factor. Landsteiner and Wiener, seeking to extend knowledge of the complexities of the agglutinogen *M* in man, immunized guinea pigs with the blood of rhesus monkeys. Surprisingly, they found that the resulting anti-rhesus serum agglutinated 85 per cent of human bloods and that the agglutinogen '*Rh*' so defined was unconnected with *M*. Almost immediately afterwards Wiener and Peters demonstrated the clinical importance of this antigen by showing that, in each of four cases where repeated blood transfusions had been followed by hæmolytic reactions, the cause lay in the sensitization of the patient to the *Rh* antigen. Levine and his co-workers then showed that the dreaded intra-group transfusions of women in the puerperium were also the result of iso-immunization to *Rh*, and they directed attention to the almost invariable association of such reactions with death of the fœtus or the occurrence of icterus gravis neonatorum. They produced striking statistical evidence that in these cases the *Rh* negative mother became sensitized during pregnancy to the *Rh* antigen in the blood of her fœtus and formed *Rh* antibodies.

Prof. Cappell suggested that the term *Rh* factor should be reserved for the antigenic component common to man and the rhesus monkey, and the term *Rh* blood group should be used to include the whole complex of antigens which had been shown to occur together in different combinations in man. Prof. Cappell now turned to the work of Prof. R. A. Fisher and emphasized that it was he who had first recognized the pattern behind the complex reactions within the *Rh* groups. Fisher first noted that the reactions of different bloods with two of the four *Rh* sera then discovered were antithetical, and he postulated that the alternative reactions were due to the presence of an antigen *C* in some bloods and of an allelomorph *c* in others. Fisher postulated the existence of two other pairs of allelomorphic antigens, *D* and *d* and *E* and *e*, which determined positive or negative reactions with the two other kinds of sera then known, which he called anti-*D* and anti-*E*. He predicted the discovery of two further antibodies, anti-*d* and anti-*e*, and the correctness of his entire conception was soon demonstrated when these predictions were fulfilled. Fisher's original scheme had had to be extended since Race's discovery of further allelomorphs C^w, C^u and c^v at the *C*/*c* locus and Stratton's discovery, recently extended by Race, of further allelomorphs at the *D* locus.

Prof. Cappell emphasized the importance of a pure anti-*D* serum for classifying bloods as *Rh* positive or negative. For clinical purposes the important thing was whether a person was *D* positive or negative, for all *D* negative persons could form anti-*D*, and sensitization to *D* was far commoner than sensitization to the other *Rh* antigens. Thus, a person of type *Cde*/*cde* might at one time have been considered *Rh* positive because of the possession of *C*;

but such a person was just as liable as one of type *cde/cde* to form anti-*D* and should be considered as *Rh* negative.

Iso-immunization of an *Rh* negative mother rarely occurred to a sufficient extent during a first pregnancy to produce hæmolytic disease of the newborn, but the second or subsequent *Rh* positive offspring might be affected. Prof. Cappell had found that the earlier hæmolytic disease occurred in a family, the severer was its form; he interpreted this as indicating a notably greater susceptibility to immunization on the part of some women. One remarkable fact that was now fully established, but the cause of which remained debatable, was the protection against hæmolytic disease afforded by *ABO* group differences between mother and fœtus. Thus, whereas in Scotland in a random sample more belonged to group *O* than to group *A*, in a series of 56 *Rh* negative Scottish women who had formed *Rh* antibodies, it was found that 28 belonged to group *A* and only 18 to group *O*.

Turning finally to the treatment of hæmolytic disease, Prof. Cappell said that one controversial question was whether nervous sequelæ could be prevented by early transfusion of *Rh* negative blood. In his own series of thirty infants treated by transfusion of *Rh* negative blood immediately after birth or within the following twelve hours, all developed normally, both mentally and physically. By contrast, in a series treated in Glasgow between 1934 and 1944, mainly by transfusion of blood of unselected *Rh* type, about 12 per cent showed some residual nervous sequelæ. He was doubtful whether the cerebral damage which results in nuclear jaundice occurred before birth; he suggested that anoxia in the immediate post-natal period, due to difficulty in establishing respiration, might be the cause.

Dr. P. L. Mollison confined his remarks to the diagnosis and treatment of hæmolytic disease of the newborn. At the Medical Research Council's Blood Transfusion Research Unit, Miss M. Cutbush and he had, during the past eighteen months, examined fifty *Rh* positive infants born to mothers whose sera contained *Rh* antibodies. In every case the infant's erythrocytes could be shown, by the direct Coombs' test, to have antibody adsorbed on to their surface. Only three of the fifty infants failed to develop anæmia. Since some infants with a positive direct Coombs' test never developed signs of a hæmolytic anæmia and since others only developed mild signs which did not require treatment, it was necessary to try to form an estimate of the severity of each case. This was best done by examining cord blood. Among the infants with hæmolytic disease whose cord blood they had examined, about two-thirds had a hæmoglobin value below the normal range, that is, less than 15 gm. per cent; almost all had a bilirubin concentration of more than 3·0 mgm. per cent and about three-quarters showed more than 10 nucleated R.B.C. per 100 W.B.C. in the peripheral blood. These three signs of anæmia, hyperbilirubinæmia and erythroblastæmia were fairly well correlated if cord blood was examined and, taken in conjunction with other findings, enabled one to assess the degree of affection.

Dr. Mollison pointed out that hæmolytic disease killed infants at two main stages and the mechanisms were probably separate. Deaths *in utero* or within twelve hours of birth seemed always to be associated with severe anæmia; these infants might display a syndrome similar to that developed by adults with chronic severe anæmia and described by Sharpey-Schafer as the "hyperkinetic phase"; its chief features were: a raised cardiac output, a high pulse-rate and pulse pressure, a high venous pressure and œdema. They had found that a raised venous pressure was a striking feature in severely anæmic infants born alive. The second group of deaths occurred at two to four days; in these cases the infant was profoundly jaundiced and at autopsy kernicterus was a frequent finding. At present the most rational method available for trying to prevent deaths from both of these causes was premature termination of pregnancy followed by an exchange transfusion with *Rh* negative blood.

Exchange transfusion had become a relatively simple procedure since the introduction by Dr. L. K. Diamond of the technique of passing a fine transparent plastic catheter up the umbilical vein; the infant's blood was then withdrawn and replaced by *Rh* negative blood in successive stages. It was an advantage to use a slightly concentrated suspension of erythrocytes so as to leave the infant with a count of approximately 5,000,000 *Rh* negative erythrocytes per c.mm. by the end of the exchange transfusion. It was seldom necessary to have to carry out any further treatment.

Dr. Mollison stated that the overall mortality in the small series he had referred to was 28 per cent. He considered it impossible to make any worth-while comparisons with other series and mentioned the following difficulties: the small size of this and of most other series; recent changes in the diagnostic criteria of the disease; the different prognosis of different forms of the disease and the consequent important effects of selection of cases. As an example he quoted some of their own findings. The first affected infant in a family had a 92 per cent chance of recovery if its mother had never received a transfusion of *Rh* positive blood; but if she had been transfused and was thus more highly sensitized, the infant's chance of survival was only 50 per cent. An undue proportion of transfused mothers in a series of cases would thus greatly increase the mortality. He considered that exchange transfusion should be given a widespread trial because it was a rational treatment and because in practice it had proved to be the most simple and satisfactory method available.

Dr. R. R. A. Coombs described work carried out in the Department of Pathology at Cambridge which had established the occurrence of hæmolytic disease in newborn thoroughbred foals; this disease, like the human one, was due to iso-immunization of the mother during pregnancy against a blood group antigen present in the erythrocytes of her offspring. This work followed on that of Caroli and Bessis, who last year had shown that the icterus of newborn mules was also due to iso-immunization during pregnancy.

Dr. Coombs emphasized that the present investigation had been undertaken by a team. The clinical studies were made by Mr. Parry, scientific officer of the Animal Health Trust, and Messrs. Day and Crowhurst, veterinary surgeons at Newmarket; the hæmatological examinations had been made by Dr. Hoogstraten; the morbid histology had been studied by Dr. Hinde and the serology by Dr. Heard and himself.

Clinically, the foals were normal at birth; thereafter at periods varying from a few hours to five days, they showed progressive weakness, icterus and pallor, accompanied in acute cases by hæmoglobinuria.

The serological investigations had been greatly complicated by a lack of knowledge of the blood groups of horses and by difficulty in obtaining blood samples from the sires of the affected foals. However, they had tested the sera of all the mares, the offspring of which were affected, against the red cells of other mares and of various other available horses. They had found that most of the sera contained high titre saline agglutinins acting on various other horse bloods and all contained blocking antibodies, revealed by the indirect antiglobulin sensitization test. None of the control sera contained more than traces of iso-antibodies.

As in the human disease, the direct anti-globulin sensitization test had proved extremely valuable in making a rapid diagnosis. Hæmolytic disease in newborn foals had to be differentiated from bacterial septicæmia which might also cause jaundice. They had tested six cases of hæmolytic disease, all of which had given strongly positive tests, and two cases of septicæmia, both of which had given negative tests. The reagent they had used was a rabbit anti-horse globulin serum.

The hæmatological picture was one of profound anæmia, with hæmoglobin levels of only 3–4 gm. per 100 ml. Nevertheless, very few reticulocytes and no erythroblasts were seen in the peripheral blood.

One of the most interesting features of the morbid histology was an extension of tubular epithelium into the glomeruli in three cases which had shown hæmoglobinuria; similar changes had been observed in 'traumatic anuria' in man.

Finally, Dr. Coombs mentioned some work which Dr. Heard is conducting. This is an attempt to produce hæmolytic disease in rabbits. There was every reason for hoping that this work would be successful and there was no need to stress the advantage that would result from having a laboratory animal in which the disease could be produced at will. Many problems of hæmolytic disease could only be investigated by experiment and could therefore never be tackled directly in man. P. L. MOLLISON

GENETICAL STRUCTURE OF PLANT POPULATIONS

A SYMPOSIUM on the "Genetical Structure of Plant Populations" was held at the Brighton meeting of the British Association for the Advancement of Science, on September 13, in Section K (Botany), with Col. F. C. Stern in the chair. Dr. W. B. Turrill (Kew), in an opening paper, defined a population, as the term should be used in biology, as the sum total of individuals of a stated kind, in a stated area, at a stated time. The need of careful determination of 'kind' and the desirability of preserving proper voucher specimens where there is the slightest possibility of determinations being called in question were emphasized. The extensive and intensive studies now being completed on numerous populations of a limited number of species of seed-bearing plants of the European flora have revealed an unexpected wealth of variation in structure and behaviour. At Kew and Potterne, investigations combining the methods of modern taxonomy, cytogenetics and ecology are throwing much light upon the make-up of species as population complexes. Attention was directed to the bladder campions (*Silene maritima* and allied species). In these some variations are common, as degrees of indumentum in *S. cucubalus*, others are rare, as long cylindrical calyx in *S. maritima*. Some characters have obvious survival value for definite ecological habitats, such as habit differences between different species or varieties. Spasmodically occurring mutations may be lethal or harmful in various degrees, like 'poor petal' or 'split calyx', whereas other variations appear to be neutral at least in some environments. Some variants have a wide geographical range while others are restricted to very local habitats. Hybridization experiments on a very extensive scale have shown genetic differences for most of the variations; but whereas some characters have a simple genetic basis others can only be explained by the interaction of several genes. Long-isolated populations of relatively small size (as some inland populations of *S. maritima*) may show much less variation than is normally found in more widely spread populations. Parallelism between sea-coast and high-mountain populations of different species is very striking.

Mr. J. L. Crosby (Durham) dealt with intra-population heterogeneity and the breeding range of the individual plant. In the primrose (*Primula vulgaris*), in addition to reciprocally outcrossing plants with 'pin' and 'thrum' flowers, there are, in certain populations in Somerset and the Chilterns, plants with 'long homostylous' flowers which are normally self-fertilized and outcross on to pins. Observation agrees with theoretical conclusions that 'homostyles' are increasing to about 80 per cent, 'pins' are decreasing to about 20 per cent, and 'thrums' are entirely disappearing. Slow at first, change later becomes quite rapid. Considerable heterogeneity between different parts of any one such population may exist. A few yards only may separate groups with constitutions so different that they represent evolutionary stages many generations apart. Such large differences cannot have arisen in one generation by chance from a homogeneous population but must have been initiated at an early stage. One section of the population reached the stage of more rapid change and the difference then became amplified. The change could not, however, even be maintained with free distribution of pollen between the divergent groups, even though 'homostyles' are self-pollinated. The breeding range of the individual primrose must be of the order of a few yards only, and a single population cannot be considered as a continuous interbreeding unit.

Dr. A. J. Bateman (John Innes Institution) considered populations of cultivated plants. He pointed out that the breeding system of the species is of paramount importance in determining the genetical structure of a population. The total range of breeding systems is from complete self-fertilization as in barley to complete cross-fertilization as in cabbage. Subordinated to the breeding system are selection intensity, population size, and gene dispersal. Heritable variation would be at a minimum in a pure line; but varieties of self-fertilizing crops are rarely represented by pure lines. The different causes of variation within varieties which should be pure lines are: (*a*) residual hybridity of the original variety; (*b*) mutation and structural change; (*c*) seed admixture; (*d*) cross-pollination. Cultivated plants show a continuous range in breeding systems from self-incompatibility and dioecism giving full outbreeding, to regular self-pollination and vegetative reproduction, giving full inbreeding or its equivalent.