Perspectives

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Quantitative Genetics in Edinburgh: 1947–1980

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FOOD rationing in the second world war brought home to everyone in Britain the need to improve agricultural output in order to reduce our dependence on imports. Seeing clearly the need for more government-funded research on animal breeding, the Agricultural Research Council (ARC) set up, in 1945, the Animal Breeding and Genetics Research Organization (ABGRO). The "Genetics" in the title signified the intention to pursue basic genetics with experimentation on laboratory animals, to be done by the Genetics Section of ABGRO. R. G. WHITE, then Professor of Agriculture in the University of North Wales at Bangor, was appointed Director, with C. H. WADDINGTON as Chief Geneticist in charge of the Genetics Section. WADDINGTON, then aged 42, was preeminent among the few geneticists in Britain at that time; his influential text, *An Introduction to Modern Genetics*, had been published in 1939. Soon after his appointment to ABGRO, WADDINGTON was offered the Buchanan Chair of Animal Genetics in the University of Edinburgh in succession to F. A. E. CREW. This was the reason it was decided to locate ABGRO in Edinburgh. WADDINGTON then held both positions, University Professor and Honorary Director of the Genetics Section of ABGRO.

The Genetics Section, which had been in temporary quarters in London, moved to Edinburgh in 1947. It was housed together with the University Department in a building named the Institute of Animal Genetics. The main part of ABGRO was accommodated in a large rented villa not far away until a new building on the University campus close to the Institute was opened in 1964.

The location of ABGRO in Edinburgh continued a distinguished tradition of animal breeding and genetics there. There were then (I think) only three university departments of genetics in the United Kingdom: London's University College (where J. B. S. HALDANE was Professor), Cambridge (with R. A. FISHER), and Edinburgh (with F. A. E. CREW). Edinburgh's department was the first, established in 1919 as the Animal Breeding Research Department, with CREW as its Director but no other staff and no building. A forceful and persuasive speaker, CREW obtained money from various sources to expand the department, and he cajoled several wealthy industrialists into providing funds for a new building and to endow a chair. The Chair, founded in 1928 with CREW as its first occupant, was called the Buchanan Chair after Lord WOOLAVINGTON whose family name was Buchanan and whose business was whisky distilling; half the funds needed for the endowment were his gift. The title of the Chair was Animal Genetics, but it was changed to Genetics in WADDINGTON's time. The new building was formally opened in 1930 with 12 scientific staff and 13 visiting researchers.

CREW's enthusiasm attracted many visitors who came for short visits or for longer periods of research, among whom were some notable figures–LANCELOT HOGBEN, JULIAN HUXLEY, J. B. S. HALDANE, and H. J. MULLER (who was there from 1938 to 1940). On a handsome oak panel in the entrance hall of the Institute building in gilded carved letters are the names of those who obtained higher degrees from the Department. There are 66 up to 1947, and 5 more by 1950 when the inscriptions stopped. The first is CREW himself who is recorded as obtaining a D.Sc. in 1921 and a Ph.D. in 1923. Others who will be familiar to most geneticists are F. B. HUTT (Ph.D. 1929, D.Sc. 1939), CHARLOTTE AUERBACH (Ph.D. 1935, D.Sc. 1947), and H. J. MULLER (D.Sc. 1940).

Under CREW's leadership the Institute did pioneering work on sex determination, reproductive physiology, and many aspects of the husbandry and breeding of sheep, cattle, pigs, horses, and poultry. There was also work on cytology, on Drosophila genetics, and on the genetics of the color of budgerigars. (When I was a Ph.D. student in the Zoology Department in

Cambridge I found a set of CREW's budgerigar skins hidden away in a drawer. They made an impressive and beautiful illustration of all the main Mendelian principles, and were a major stimulus to my own interest in genetics.) CREW's era culminated in the holding of the Seventh International Congress of Genetics in Edinburgh in August, 1939. He was made President in default of N. VAVILOV who was unable to come (see the *Perspectives* of August, 1992). The outbreak of the second world war brought the Congress and most of the Institute's activities to an abrupt end. During the war CREW, who had a medical degree, worked in the War Office on medical statistics. He resigned his Chair in 1944 because, so he said, he felt himself to be too much out of date in genetics, but he returned to Edinburgh to take up the Chair of Public Health and Social Medicine.

When the ARC group came to Edinburgh after the war, CREW's Institute was much depleted in staff and funds. Soon after arrival in Edinburgh one of our technical staff, not renowned for his tact, found himself sitting next to an unknown person at coffee and, thinking that some conversation was called for, remarked, "I understand that this place has been pretty inactive recently." The unknown person was A. W. F. GREENWOOD who had been acting Director during CREW's absence. It is no wonder that those left of CREW's staff saw us newcomers as an arrogant lot intent on an aggressive take-over. I fear that at first we were a sore trial to them.

The ARC funded agricultural research in two main ways. There were large groups in their own buildings with a full-time director appointed by the ARC, and there were "units" which were small groups working in a university department under the direction of a senior member of the university staff, usually the professor. ABGRO was a large group, but the Genetics Section operated like a unit within it; its members were ABGRO staff but WADDINGTON, its director, was not. This anomalous situation was rectified in 1951 when H. P. DONALD, who had been in CREW's department, succeeded WHITE as Director of ABGRO. The Genetics Section was then formally separated; ABGRO lost its G and became ABRO. In 1957 the Genetics Section was designated the Unit of Animal Genetics.

In what follows I shall not discriminate between the Genetics Section and the Unit, and will refer to both as the Unit. It is about the Unit that I am writing here and I will not be able in this short article to say more about ABRO, though there was much fruitful collaboration between the members of the two groups, and the work of ABRO was a large component of quantitative genetics in Edinburgh.

To review adequately the work of the Unit would be impossible. Instead I shall summarize briefly the earlier work done by its members. Those in the Unit at the beginning in 1947 who worked on quantitative genetics and related topics were the following:

C. H. WADDINGTON. His many diverse interests centered on developmental genetics. In quantitative genetics, he showed with Drosophila how what looked superficially like Lamarckian inheritance of an acquired character could result from straightforward selection.

ALAN ROBERTSON. With J. M. RENDEL he formulated improvement programs for dairy cattle, and the "contemporary comparison" by which bulls are selected for use in artificial insemination, which revolutionized dairy cattle breeding. His experiments with Drosophila tested the adequacy of current selection theory and located some of the genes responsible for the responses to selection, foreshadowing contemporary quantitative marker identification. Using KIMURA's stochastic theory, he developed a new theory of selection limits in a finite population.

J. M RENDEL. After working with ROBERTSON on dairy cattle, he left in 1951 to join CSIRO in Australia and became head of its genetics section. He is well known for his work on developmental canalization in Drosophila.

D. S. FALCONER. I showed that selection for growth in mice was most effective when practiced in the environment in which the strain was expected to perform (as opposed to the frequently advocated practice of selecting in the most favorable environment), and that a character measured in two environments could be treated as two correlated characters. I introduced the use of realized heritability as a way of describing selection response.

R. A. BEATTY. In addition to studies of heteroploidy in mice and rabbits, he studied the genetics of spermatozoa, showing that metric characters of spermatozoa are determined by the genotype of the testis and not that of the spermatozoa.

F. W. ROBERTSON. In selecting for large and small body size in Drosophila he found strong asymmetry in the response to selection in the two directions, and showed that at the selection limit there was still considerable genetic variation. Chromosome assays of selected lines revealed strong epistatic interaction. Differences of body size were due to differences of cell number, not cell size. Later he worked on the ecological and physiological genetics of Drosophila growth. In 1970 he left for a chair in Aberdeen University.

E. C. R. REEVE. He worked with F. W. ROBERTSON on selection in Drosophila and showed that inbred lines were considerably more variable than F_1 hybrids. Later he worked on bacterial genetics.

J. H. SANG. He studied population growth of Drosophila in culture, and developed a synthetic culture

medium which became an essential tool for physiological genetics. He left for a Chair in the University of Sussex in 1965.

Some later appointments in quantitative genetics were:

N. BATEMAN (1948). He selected for high and low milk production in mice and found very strong asymmetry of response. He transferred to ABRO in 1957.

I. L. MASON (1949). He studied dual-purpose cattle and advised on animal breeding programs in many countries. He cataloged the origins and characteristics of all livestock breeds. In 1972 he left to join FAO in Rome.

G. A. CLAYTON (1950). He worked with A. ROBERTSON on Drosophila selection and fitness experiments. They were, I think, the first to select with replicate lines and to test the observed responses against theoretical predictions. He also worked on turkey breeding. He transferred to the University staff in 1959.

A. L. MCLAREN (1958). She studied maternal effects, embryo transfer, early development, reproductive physiology, and chimeras in mice. In 1974 she left to be Director of the Medical Research Council's new Mammalian Development Unit in London.

R. C. ROBERTS (1959). He compared the life-time growth and reproduction of mouse lines selected for large and small body size and found that small mice had smaller litters, but more of them, than large mice, and produced nearly twice as many offspring in total. He characterized selected mouse lines using A. ROBERTSON's theory of selection limits.

W. G. HILL, who was appointed to the University staff in 1965, must be included here because he worked in close association with the Unit. His work covered many aspects of theoretical quantitative genetics, particularly in relation to selection and the estimation of parameters.

It was never the intention that the work of the Unit should be restricted to quantitative genetics. WADDINGTON believed, as CREW had, that any aspect of genetics might lead to advances in animal breeding. Accordingly there were other members of the Unit working on molecular genetics, cytology, development, and systematics, among whom were H. G. CALLAN who went to a chair at St. Andrews University in 1950 and J. L. SIRLIN from about 1962 to 1970.

We were generously provided with excellent technical assistance. A great advantage of working in the ARC. Unit was that funding was always assured; we did not have to spend time writing grant applications.

By the 1940s, partly because of the war, Britain had fallen far behind the United States in quantitative genetics and the theory underlying animal breeding. In the United States, J. L. LUSH's *Animal Breeding Plans* had been published in 1937, but the principles it set forth were virtually unknown in the United Kingdom despite the presence of HALDANE and FISHER who had provided much of the mathematical background. There were few geneticists of any sort, and they tended to be regarded as eccentrics pursuing an incomprehensible subject. Consequently little or no genetics was taught in undergraduate courses. Most of us, therefore, joined the Unit with very little background in genetics. For example, the nearest thing to genetics in my zoology course at St. Andrews was the curious fact that Ascaris sheds most of its chromatin when it makes somatic cells. Some of us had not even a biological background; ALAN ROBERTSON started as a physical chemist, and REEVE as a mathematician. After joining the unit, however, ROBERTSON spent nine months with SEWALL WRIGHT and J. L. LUSH, the two who had done most to develop quantitative genetics in its application to animal breeding. Consequently, he was much better informed about quantitative genetics and animal breeding than the rest of us. In preparation for joining the Unit I spent 18 months with R. A. FISHER in Cambridge in order to learn about mouse genetics. FISHER was then mainly interested in linkage, and I did not learn much about quantitative genetics from him.

The original intention for the work on quantitative genetics was that there should be research on farm animals (but without farm facilities), on rabbits, on mice, and on Drosophila. The basic quantitative genetics would be done with Drosophila because it is cheap and quick. But the results from Drosophila could not be applied directly to farm animals because Drosophila is too different in physiology, in chromosome number, and in lacking crossing over in males. The rabbits and mice were to form a bridge, being similar in physiology, chromosome number, and male crossing over. Any breeding method that might be based on the Drosophila results would be tried with mice or rabbits and if it worked it could be applied with more confidence to farm animals. It soon became apparent, however, that there was no great difference in the quantitative genetics of Drosophila and mice. So the chromosome number, male crossing over, and indeed the physiology, were largely irrelevant.

No one "directed" our work. The ARC itself seemed to take no interest in what we did, or what we achieved. WADDINGTON, nominally our director, left us free to do what we each thought best. This was a wise policy, and it worked; I do not think that any of us wasted much time in doing the wrong things. And the freedom was greatly appreciated.

The first experiments done with Drosophila and mice were on selection. These take a long time, and when they finally produced results we were eager to publish them quickly. But in this we were frustrated. We sent the papers to the *Journal of Genetics*, the

oldest of the two British journals publishing genetical work. It was owned and edited by J. B. S. HALDANE, who did the refereeing himself. But he was not well organized. It was said that when he was away for some time the cleaners, unwilling to disturb the piles of paper on his tables, covered them over with newspapers. When he returned he did not remove the papers, but started again on top. This was very useful to the geologists who, when HALDANE was away, took their students to his room to demonstrate stratification. It required several pleading letters of reminder before we eventually got our papers published. Continued difficulties with publication in British journals led WADDINGTON to found a new journal, *Genetical Research*, in 1960. Edited by E. C. R. REEVE, it has flourished and earned a high reputation.

In 1948 I. M. LERNER, a visitor from California, brought us new techniques from the United States. He unfolded the mystery of SEWALL WRIGHT's path coefficients, which were being used for deducing the necessary theoretical parameters for quantitative breeding. LERNER wrote most of his *Population Genetics and Animal Improvement*, published in 1950, while he was in Edinburgh. An important event in 1949 was a visit by SEWALL WRIGHT who also spent a sabbatical year in Edinburgh. I think, however, that his visit came too soon for some of us who did not have enough background to understand much of what he had to teach us, though it was a useful stimulus in showing us what a long way we had to go to catch up with current knowledge. He gave a long course of lectures and these formed the basis for part of his *Evolution and the Genetics of Populations*, the first volume of which was published in 1968.

In 1950, near the end of WRIGHT's visit, a symposium on quantitative inheritance was held in the Institute; it was published in 1952. WRIGHT gave a lengthy talk on the interactions between coat color genes in guinea pigs. But the manuscript was lost on his way home and a quite different paper appeared in the published symposium. It was a synopsis of the current state of quantitative genetics and was surely more generally useful than the guinea pig paper would have been. The symposium, however, had unforeseen and regrettable consequences of a political nature. KENNETH MATHER, then Professor of Genetics in Birmingham, was invited and talked about his chromosome-balance theory of quantitative inheritance. This asserted that + and − genes (those increasing and decreasing the trait) are arranged in repulsion linkages. The net effect of a chromosome is minimal but it holds a large amount of hidden variation that can be released by recombination. His theory was not well received by the audience and he was criticized in a forthright but injudicious manner. MATHER, as a guest speaker considerably senior to us, was understandably affronted. I believe that the cool relationship between the Birmingham and Edinburgh schools that persisted for many years may have had its origin in this unfortunate episode.

The members of the ARC Unit, though ostensibly employed for research, contributed substantially to the Department's teaching. In respect of what we actually did in the Institute, there was little distinction between Unit and University staff, and those not familiar with the local arrangements often did not know to which group anyone belonged. The University authorities, however, were slow to recognize the existence of non-University staff and subjected us to petty restrictions. For example, we could not be official supervisors of Ph.D. students; there had to be a University supervisor, usually WADDINGTON who often knew little or nothing of what the student was doing. Eventually, however, the authorities were persuaded to be less narrow-minded. In 1949 a postgraduate Diploma in Genetics was started, allowing students with little previous training in genetics to embark on Ph.D. studies; it had a substantial component of quantitative genetics. Then, in 1975, an M.Sc. in animal breeding was started in collaboration with the Agriculture Department and was run by W. G. HILL, who had worked on animal breeding and had become a leading theorist in quantitative and population genetics. This was the only course of its kind in the United Kingdom. It attracted students (about six each year) from all over the world, many of whom went on to take Ph.D.s in Edinburgh and then went home to found nuclei of quantitative genetics or animal breeding in their own countries, notably in Australia and New Zealand. Not surprisingly, many of the staff of ABRO or its successor organization were recruited from among our students.

The Institute housed much more than just the ARC Unit. WADDINGTON rapidly increased the staff and the range of research, and there were several groups of workers with separate funding. The following is a very incomplete outline of the research staff of the Institute in the early 1960s, when the numbers were probably near their peak. The Unit then had nine staff members, and the University 13, among whom were the following. CHARLOTTE AUERBACH had been a research assistant to CREW; during the second world war she discovered the first chemical mutagen, mustard gas, and opened up a whole new field of research. G. H. BEALE worked on Paramecium, and later developed the new field of the genetics of the malarial parasite. H. KACSER studied the genetics and enzymology of metabolic pathways. B. WOOLF helped many people with his statistical advice, and was the originator of the idea of realized heritability. W. G. HILL's work has already been outlined. A later addi-

tion was D. J. BOND, who worked on fungal development.

From 1947 till 1955 there was a group of four, funded by the Medical Research Council (MRC), working on the mutagenic effects of radiation on mice. This was an outpost of the MRC's Radiobiology Research Unit at Harwell in Oxfordshire. Among its members were T. C. CARTER, who later became director of the ARC's Poultry Research Center, and M. F. LYON, known for her work on *X* inactivation and the *t* locus in mice. Then, in 1958, the MRC set up another group, the Mutagenesis Research Unit, of which AUERBACH was director. It had five members among whom were B. M. CATTANACH and B. J. KILBY. And finally, in 1963, the MRC founded the Epigenetics Research Group under WADDINGTON's direction with M. BIRNSTIEL as his deputy. There were initially four MRC staff in the group, but others with different funding worked in the group, among whom were K. W. JONES and, from the University staff, J. O. BISHOP, R. M. CLAYTON, J. JACOB, A. JURAND and G. G. SELMAN. The group worked on development and molecular genetics.

WADDINGTON was an inveterate traveler and was widely known throughout the world. His interests were wide-ranging, and not only in science. Among his 17 books was a lavishly illustrated one showing how modern art had been influenced by the ideas of science (WADDINGTON 1969). WADDINGTON's breadth of interests, and the reputation of the Institute, attracted many visiting research workers and Ph.D. students, so that there were usually more visitors than indigenous staff. New people seemed to be arriving almost every day and it was hard to keep track of who was who and doing what. An idea of the numbers can be got from a list of people present in June, 1962. There were 22 permanent staff and 36 temporary research workers. The visitors came from 13 different counties in addition to the United Kingdom. Their fields of work are recorded as: development (12), quantitative genetics and animal breeding (10), mutation (7), Paramecium (4) Neurospora (2), and gametes (1). With so many people of such diverse interests the Institute was a lively and stimulating place. It was a great privilege to work there during that time. Naturally, lots of papers were published. In the period 1961–1965 there were an average of 85 papers and 8 Ph.D. theses per year.

Meeting for coffee in the canteen was an important activity which kept staff and visitors in touch with each other. Some might say that this was a waste of research time, but it was not; often we got valuable ideas and advice. At first nearly everyone came, but later, as we got to know each other, the meetings broke up into specialist groups. Of these, ALAN ROBERTSON's coffee sessions became world famous and continued until his final illness. He died in 1989; his personality and wisdom are greatly missed.

Did WADDINGTON keep in touch with all the many staff and visitors? With the permanent staff he did, to some degree. We in the Unit seldom had any conversation with him, yet he often surprised us by knowing what we were doing and what we had found. He did this mainly, he said, by reading our papers. Of most of the visitors, however, he knew very little. It was not unknown for a visitor to have spent three years in the Institute and never to have spoken to him. Many of the Ph.D. students came expecting to work under WADDINGTON's supervision. But often he was away on his travels, and then the rest of us had to come to the rescue, hastily think up suitable projects, and find space and facilities for them.

Although WADDINGTON seemed to take little day-to-day interest in what we did, he took great pride in the achievements of his staff. He was immensely proud of the fact that in 1975 there were five Fellows of the Royal Society among the Institute staff (WADDINGTON, AUERBACH, BEALE, A. ROBERTSON, FALCONER) with a sixth (MCLAREN) being elected shortly after leaving. HILL was elected after WADDINGTON had died. This was out of a total of about 19 in the whole University and it elicited an article by a columnist in a newspaper (TAYLOR 1975) in praise of the Institute.

Most organizations go through a cycle of growth and decline. The Institute was no exception. There were three reasons why it grew the way it did: first, and most important, WADDINGTON's drive to expand; second, the ready availability of funds at the time; and third, good fortune in the selection of staff. It reached the peak of its activities in the late 1960s and then started a gradual decline, for which I can see several reasons. Possibly the prime reason was that WADDINGTON's interests moved from genetics and the Institute to futurology. In 1970 he went for two years to the Center for Theoretical Biology at Buffalo, and when he returned he set up a new "School of the Man-Made Future" in the University. In consequence he was seldom seen in the Institute from then till his death in 1975. Fewer visitors came. Interest in most areas of research was shifting to the more molecular. Embryo transfer and, later, the prospect of transgenic animals made classical quantitative genetics of less interest to animal breeding. Working in Edinburgh had been so attractive that few staff members had moved elsewhere. Consequently most of us were of an age when change becomes difficult. Funds were increasingly hard to get and, in the absence of new posts, very few young people could be recruited to rejuvenate the Institute.

To complete the history: before he went to Buffalo WADDINGTON wanted to shed his responsibilities in the Institute and in 1968 he resigned as Director of

the Unit. I was made Director in his place and at the same time was transferred to the University Department in a personal chair; a year later I was made head of the Department and held this position until J. R. S. FINCHAM came to the Buchanan Chair in 1977. T. F. C. MACKAY joined the Department in 1980 when I retired. ARC Units are normally terminated when their directors retire. That our unit survived a change of director may have been due partly to its beginning as part of ABGRO and partly to the ARC's difficulty in finding new posts for its members. It did not, however, survive my retirement. By then most of its members had left or retired, and the Unit was finally terminated in 1980. Very fortunately W. G. HILL was on the University staff and was not directly affected by the closure of the Unit. A new cycle of quantitative genetics has started under his leadership, with a new and strong group.

I am very grateful indeed to R. C. ROBERTS and W. G. HILL for reading the drafts and offering many helpful suggestions, and to B. JAMIESON of the AFRC (formerly the ARC) for supplying some dates. I ask forgiveness of any of my colleagues who find errors, omissions, or misunderstandings.

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