The Principles of Humane Experimental Technique

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CHAPTER 7

REFINEMENT

... endless forms most beautiful and most wonderful have been, and are being evolved.

A Concrete Problem: Experimental Psychiatry and the Humane Study of Fear

Experimental Psychiatry and the Screening of Tranquilizers

The recent rapid progress of neurochemistry and neuropharmacology have increased the importance for psychiatry of experimental work on animals. We are faced with a battery of new drugs acting upon the brain, and with the possibility of developing both more and better ones.

The most famous of these drugs are the so-called tranquilizers. The extremely vague specification for their common property is that of easing "anxiety and psychomotor agitation without affecting consciousness to any extent" (Shorvon, 1957). They are extremely heterogeneous both chemically and pharmacologically, and include Chloropromazine (Largactil) and its chemical relative Mephazine (Pacatal); Reserpine (Serpasil), and alkaloid derived from a plant; benactyzine compounds (Suavitil, Nutinal, Covatin); meprobamates (Equanil, Miltown and Mepavlon); and hydroxyzine compounds (Atarax). All have come into use in the fifties, and all except Reserpine are synthetic (Shorvon, 1957). Chlorpromazine and Reserpine seem to be related pharmacologically to the hallucinogenic drug lysergic acid, and all three to the substance serotonin found widely in the body and having important vasomotor properties, but it is doubtful if interactions of this kind account entirely for the central nervous effects (cf. e.g. Bianchi, 1957; Bonnycastle *et al*, 1956; Vogt, cited in Anon., *Nature*, 1956c). Some of the tranquilizers, notably chloropromazine, have marked actions on the hypothalamus, and hence on all six adenohypophyseal hormones and their targets (Sulman and Winnik, 1956). Despite the serious effects of some of them (e.g. jaundice, Parkinsonism, and severe depressions), many of these drugs are already being used clinically on a remarkably wide scale, especially in the United States; 5-10% of all prescriptions in New York City in March, 1957, were said to be for tranquilizers. It is estimated that about 35 million prescriptions for them were written in 1956 in the United States. Attempts are now being made to control their use. The most popular of all, Miltown, has become the fourth most commonly prescribed drug in America, "and there is no doubt that Equanil, the same drug in England, is greatly in demand" (Shorvon, 1957; cf. Anon., *Nature*, 1957). The rapidity with which new tranquilizers are now being synthesized, in the "feverish search for a panacea for anxiety" (Shorvon), is considerable.

Whatever the demerits of the existing tranquilizers, the feverish search continues unabated. More generally, it is a search for new compounds with powerful effects on behavior of as yet dimly envisaged kinds. The organic chemist can oblige almost *ad libitum*, and the key problem is that of devising tests, not for the existing tranquilizers, most of which can be assayed chemically, but for the screening of a host of new compounds in search of the desired properties. A good deal is known about the present drugs neurochemically and even neurophysiologically, but no successful attempt has been made to clarify exactly what effects on behavior are involved. This urgent need is thrown into relief by the screening problem, but is no less urgent for purposes of experimental psychiatric research, which might rationalize the situation and guide the search. In both contexts, experimental animals are necessary.

We may quote some remarks of Chance (1957a) in this context.

"Now the advent of 'tranquilizers' has found us completely unprepared. The concept, although originally definable in terms of the observations made on chloropromazine, reserpine, and benactyzine, now obscures a confusion which can only become greater without a systematic knowledge of the way behavior is organized in laboratory mammals. The interest that the discovery of these substances has aroused in the screening of new substances for tranquillizing action arises from a keenly felt but poorly informed awareness that brain function can be modified by drugs in many more ways than has been suspected so far. Under the guise, therefore, of searching for 'tranquilizers' every kind of test of behavior is being pressed into service, in the scramble for new drugs with possible useful actions on the brain... Only when the manifestations of the integrative activity of the brain are recognizable from *a knowledge of the behavior of each species of animals* [our italics] will it be possible to distinguish readily between drugs producing disruption of normal brain function and those possessing a smooth selective action."

The actions of these drugs must be complex and multiple, and a variety of central nervous mechanisms must be implicated. Some of these mechanisms must be specifically mammalian, and related to all those changes in neurological and behavioral organization associated with the presence of an extensive neocortex. Others, however (at the base of the brainstem, perhaps), may be common to most or all vertebrate groups. These mechanisms may well show the remarkable chemical stability, which, as much of endocrinology testifies (cf. Medawar, 1953), we commonly find in biochemical systems designed for control functions. One thinks here of such behaviorally separable mechanisms as the flight, attack, and mating drives (fear, rage, sex), prominent in the social behavior of almost all vertebrates--for it is primarily *social* behavior that concerns psychiatry, experimental or clinical. It is the presence among those of the flight drive (or, as we also call it, *fear),* that lends special interest to the problem in the present context. What we require is a set of models which will discriminate and measure effects upon these drives, as well as models of higher fidelity which will indicate the response of the mammalian brain as a whole and its special structural and functional mechanisms. Notice that for the former purpose the non-mammalian vertebrates might well be possible candidates, though they could not necessarily replace the mammals when we wish, as it were, to put the pieces together again.

The concept of drive is susceptible of rigorously precise analysis (Russell *et al*, 1954; Russell, in press, c; Russell and Russell, in press). Any given primary drive may be expressed in a great variety of *acts.* It is such fundamental central mechanisms as primary drives which the psychiatrist is concerned to influence, rather than the particular actions in which they are expressed in individuals, the extremely diverse results of specific patterns of conditioning. If this were not so, animals would be useless as models here. Attempts have often been made in the history of psychology to abandon the notion of primary drives. Such attempts originate from a dislike of, and naïvety about, physiology and pharmacology. Those who make them choose to paint the box blacker than it really is, and theorize on the assumption that the animal or human skull is full of sawdust. The repressed concept inevitably returns, as in the notion of peripheral inputs in terms of their terseness. In all vertebrates, the acts controlled by a particular primary drive are determined partly innately and partly by conditioning. Mammals differ from lower vertebrates in a greater capacity to reverse a conditioned response; they are better at *unlearning* (Diebschlag, 1941; Russell and Russell, 1957 and in press). Man, of course, has developed a new mode of behavioral organization--that of unified intelligence; his *pathology,* and therefore the whole province of psychiatry, is ultimately a matter of conditioning-like processes, which impair, cripple, and distort the development of his intelligence (Russell and Russell, 1957). In this way (among other things) man loses control of the rhinencephalic mechanisms, painfully acquired in mammalian and primate evolution to control the primary drive mechanisms associated with older brain structures (cf. e.g. Chance and Mead, 1953; Rothfield and Harmon, 1954).

Rational use of animals for experimental psychiatry thus depends on an accurate knowledge of "the behavior of each species of animals", so that we can trace the interaction of such mechanisms as primary drives in the whole pattern of behavior of a species. We can then make use of the natural occurrence, in the lives of the animals, of the behavioral states it is desired to influence. This is an important principle for both humanity and efficiency. In fact, the emergency has thrown into prominence, as Chance points out, our extreme relative ignorance of the behavior of the commoner laboratory mammals. Recourse is, therefore, being had to a miscellany of desperate methods. Where the flight drive (fear) is concerned, a tendency is already emerging to race for the electric grid, as the most convenient Procrustean method for terrorizing rats. This is a rat race better stopped before it starts in earnest. Nor will such methods, full of flaws due to our ignorance, contribute anything useful to the problem in hand.

The Use of Lower Vertebrates

There are only two solutions to this increasingly urgent problem. One is the intensive and systematic study of the social behavior of the commoner laboratory mammals themselves. This is the approach suggested by Chance (1957a), and we have already seen how urgently it is needed for other purposes (Chapter 6). This course is desirable and necessary in any case. It is no part of our intention to oppose it. But it can be usefully supplemented, especially in the early stages, by a different approach, which well illustrates most of the principles we have urged in this chapter. There are, in fact, two natural and complementary solutions: *behavioral study of existing laboratory species, and recruitment of behaviorally well studied ones.* Our ignorance of the behavior of common laboratory mammals is offset by a wealth of knowledge about that of numerous lower vertebrate species. Many of these would make eminently suitable recruits to the laboratory. And this knowledge is concentrated on precisely those aspects of behavior likely to be of service in the screening of new neurotropic drugs. As we have seen, models discriminatory for the widespread vertebrate mechanisms of flight, attack and mating are just what we require for at least a major part of the purposes of experimental psychiatry. A great variety of such models have been made available. This is due to the progress of ethologists in the analysis of *threat* and *courtship* movements and postures of both birds and fishes into the component drives which make up their central motivation (see e.g. Tinbergen, 1952a & b, 1953a & b, 1954; Tinbergen and Moynihan, 1952; Russell, 1952; Hinde, 1953, 1954; Van Iersel, 1953; Morris, 1952, 1954a & b, 1955, 1956b[1]; Moynihan and Hall, 1954; Moynihan, 1955; Baerends *et al*, 1955; Baggerman *et al*, 1956; Marler, 1956; Spurway, 1956; Weidmann, 1956; Wood-Gush, 1956; Andrew, 1957; Forselius, 1957; Hoogland *et al*, 1957). This development owes its ultimate origin to a classical paper by Lorenz (1935); its vigorous promotion in the fifties stems from an inspired hypothesis of Tinbergen.

Threat can be dissected into flight and attack drives, courtship into those for flight, attack, and mating. Differences in the proportions of the two or three components can be accurately inferred from the qualitative and quantitative properties of the resulting movements and postures. These movements and postures, whether they arise innately or by conditioning, are exceptionally stable and stereotyped, on account of the signal function which has governed their evolution (cf. Morris, 1957). In this way, specific central mechanisms can be separately studied, often at the same time. (For the technical problem of behavior measurement, cf. Russell *et al,* 1954; Chance and Mead, 1955; Morris, 1957.) The composition and balance differ between species. Thus the role of the flight drive courtship is less marked in the three-spined than in the ten-spined stickleback, owing to the fact that the former species, better protected by its efficient spines, is less timid in general (Morris, 1955; Hoogland *et al,* 1957). (The three-spined stickleback is a territorial animal, and since the male courts in his own territory he is almost devoid of social fear, as well as of fear of predators--cf. Tinbergen, 1953a). A strong flight component is found in many species of birds, and gives rise to a definite "individual distance" (Hediger, 1955). That is, birds of such species will not normally approach each other nearer than a certain distance, characteristic for the species concerned. This may be an unavoidable generalization of a principle salutary enough in animals which can escape their predators by taking to the air, if only they have sufficient time for takeoff. At all events, birds of such species *do* have to break the rule in the breeding season, and it is this that often accentuates the flight component in their courtship. Observe here that we can thus study fear without imposing any punishment at all, and indeed merely by means of conditions which the bird necessarily encounters in the course of its normal life--specifically, when it has to approach its mate for breeding purposes.[2] It is now perhaps clear that even fear can be studied without anything we can rationally call inhumanity.

Sometimes, as in the male zebra finch, the attack drive is lowered in courtship at an earlier, separate stage. There is then left a precopulatory ceremony which is a simple composite of the flight and mating drives. Its most prominent feature in the zebra finch is the "pivot dance", in which the male approaches the female along a branch in a series of swings, which take him alternatively towards and away from her (see Fig. 9). The size of the swings in a particular direction reflect the level of the drive concerned. This species breeds all the year round, and the birds "begin to nest-build and court within minutes of their release into the aviary" (Morris, 1954, also 1956). Here is an obvious potential recruit for the laboratory ranks. A number of finch species have been studied in this way. A schoolboy recently reported a series of interesting observations on British finch species, and remarked that they were suitable for his purpose "on account of the ease with which they may be kept under conditions almost natural to them" (Hughes, cited by North, 1956).

This diagram shows the movements of the pivot dance in the male zebra finch, seen from above.

Four successive stages of the ceremony are shown--I, II, III, and IV. The broken arrows show how the male moves from one position to the next. The long bar running along the diagram is a twig on which both birds are perched.

As the figure shows, the female remains stationary, facing across the twig. The male moves towards her in a series of pivoting movements, swinging from side to side. His tail moves through an even wider arc than his body. The dance can be seen as the outcome of a conflict between *flight* and *mating* drives, the former causing the male to avoid the female, the latter to approach her. The amplitude of the swing in each direction reflects the level of the corresponding drive. For further explanation, see text.

We can thus begin to envisage the progressive specification of a drug. It does, or does not, change the balance of the zebra finch pivot dance (by an effect on the flight drive); it does, or does not, reduce the attack component in the courtship of the three-spined stickleback; and so on. For screening purposes, every different test combination is available. Sometimes both flight and attack components are missing from a courtship which, as a result, is extremely simple. This is the case, for various reasons, in male frogs and toads of many species (Russell, 1952). The male clawed frog *(Xenopus laevis)* is, for many reasons, a sterling laboratory animal, and already in use for other purposes (Table 13). In its exceptionally pure[3] mating behavior it yields a test for sex hormones which is of unique specificity (Russell, 1954). The flight drive may interfere with mating in other ways in this species, though not in other frogs and toads. Finally, in this group, neurological study has kept in step with analysis of behavior (Aronson and Noble, 1945; Russell, 1954).

This last condition is unfortunately far from met in teleosts and birds. Their status is the exact inverse of laboratory mammals. The behavior of many bird and teleost species is already richly studied, while our knowledge of the structure of their forebrains is surprisingly slim--just how slim may be inferred from the achievement of Erulkar (1955), who by employing modern techniques in a few simple experiments has been able to revolutionize our picture of the bird thalamus. The bird and teleost forebrains are strikingly different from those of mammals, except in the region of the hypothalamus (Herrick, 1924; Kappers *et al,* 1935). Their high-level behavioral organization is no less profoundly different from that of mammals (Diebschlag 1941; Russell *et al,* 1954; Russell and Russell, in press). For two reasons, our neurological ignorance need not disqualify lower vertebrate recruits. First, there is no ground for supposing any radical differences between mammalian and non-mammalian vertebrates in the basic drive mechanisms we have discussed. Second, the entities studied by psychiatrists are behaviorally and not neurologically defined. Hence we need not hesitate to use lower vertebrate species as functional models.

Many birds present a more practical obstacle. The very timidity that issues in individual distance has an unfortunate consequence--the trauma of injection is liable to cause behavioral disturbance sufficiently prolonged to interfere with the proposed tests. But the use of aerosols would overcome this obstacle, and if birds dictated the development of this technique, they would confer a benefit on experimental animals of all species.

This sketch may show that, by judicious choice of species and due consideration of their natural behavior, a great and urgent pure and applied research problem might be tackled successfully. We do not discount Chance's proposal to study systematically the existing laboratory mammals. This would confer a host of benefits, and is wedded to the same principle. By all means let us find out what part these same mechanisms play in the ordinary course of life in the mouse and rat. For instance, tranquillization might overcome the resistance of the rat to exploring new terrain outside its base--a resistance which appears without any previous punishment. What we wish above all to emphasize is that by such methods we can overturn the paradox and study fear without humanity.

All these suggestions were made at the UFAW Symposium on Humane Technique in the Laboratory, held on the 8th of May, 1957 (Russell, 1957b). Dramatically enough, it was on the very next day (9th of May) that Eckhard Hess published an important paper on experiments with mallard ducklings (Hess, 1957). In the course of these experiments, he showed conclusively that meprobamate and chloropromazine reduce or eliminate flight reactions in this *bird* species. The drugs, incidentally, were given by the oral route, so the trauma difficulty mentioned above did not arise. We shall not discuss in detail Hess's profoundly interesting work, on which comment has been made elsewhere (Russell and Russell, in press). Three observations will suffice. First, Hess has provided yet another behavioral situation which could be used for the test purposes we have discussed. Second, the fear he was able to alleviate was not induced by previous punishment, but was an inevitable feature of the life of a duckling. Third, there is some ground for supposing that the most dramatic effect of meprobamate--the prevention of the very rigid conditioning process called imprinting--was due to the suppression of a latent fear not expressed in any overt action. If this interpretation is correct (it is not that of Hess) the implications for human psychopathology are prodigious. The whole situation may be of special interest as an illustration of the ideas we have put forward, and might afford a particularly humane test.

For our present purposes, fear is the most important of the mechanisms discussed. It does no harm to have many alternative suggestions ready; on the contrary, this is a natural outcome of the list-making activity we have recommended. We shall, therefore, close this chapter with yet another possibility of achieving the same object--the humane study of fear (see again Russell, 1957b). Thus, we may show how many degrees of freedom are available even in this most delicate of investigations. In its recruiting campaign, experimental psychiatry would be ill-advised to look the humblest gift-finch in the beak. But the animal we shall now consider is the homely pigeon, already a member of that existing non-mammalian 5%. We obtain this instance from the beautiful experimental work of Diebschlag (1941), a refiner if ever there was one.

Diebschlag was trying to train his pigeons to perform certain simple tasks. Specifically, he wished them to choose one of two platforms in front of their cage. He found that the birds could soon be trained to mount a platform in search of food, which was provided on top of the platform in a dish, invisible until the platform was mounted. His next problem was to find how to make the pigeon *avoid* a given platform. To begin with, he simply put no food on this forbidden platform. This was useless, for the pigeon would simply try the right platform first, once it had been trained to do so, and then fly to all the other "forbidden" ones, as if to make sure there was no food there as well. It continued to repeat this procedure over many trials. So absence of food did not prevent the bird from visiting the forbidden platform repeatedly. Diebschlag now tried to scare the bird when visiting the forbidden platform, by means of a sort of scarecrow. This was a fiasco. After a few such scares, the birds would not visit any platforms at all, and stayed in their cages. Instead of resorting to new and worse scares (as, one feels, some experimenters might have done), Diebschlag now hit on a simple expedient. He placed on the forbidden platform a dish of food covered with a transparent plate. A pigeon arriving there would now make a number of fruitless pecks, and finally give up. This time it did succeed in learning not to visit the frustrating platform. Diebschlag used this punishment-free method throughout one of the most important learning studies ever performed, and the story is already instructive enough for those wishing to study learning in birds.

But an interesting by-product now emerged. In some of his experiments, Diebschlag wished to *re*train his birds. For instance, after learning to mount the left-hand platform and avoid the right-hand one, the bird would now be expected to learn exactly the opposite. To bring this about, Diebschlag put accessible food on the right-hand, and inaccessible food on the left-hand platform. In order to get the food, the birds had now to mount the platform it had hitherto learned to avoid. This retraining proved surprisingly difficult. For the first three trials, such a bird made futile efforts on the left-hand platform, and *never* approached the one it had learned to avoid. In order to bring about retraining, Diebschlag had to bring the two platforms so close together that a hungry bird, standing on the left-hand one, could actually see the food on the right-hand one. After hesitating for minutes, such a bird hopped gingerly over to the formerly forbidden spot. It ate here with marked uneasiness, and a small sudden noise was enough to make it take to flight in panic. After one such experience, the bird would be even more hesitant in approaching the formerly forbidden platform, and would sometimes try to reach it from the "safe" one by stretching as hard as it could. In short, once the bird had been frustrated on a given platform, that platform was tabu, and a place of terror.

In the light of some other observations, Diebschlag was able to interpret this curious result. Apparently, once a bird had been frustrated in a certain place, it henceforward regarded that place as part of the territory of a rival bird. The terror it showed was, therefore, terror of an imaginary rival. The slightest noise seemed to threaten an immediate return of the owner, and sent the trespasser flying for the safety of his own familiar territory. The degree of fear shown becomes intelligible when we recall that birds of this family are peculiarly merciless and ferocious fighters. They have evolved no effective means of inhibiting attack, since they normally seek safety from each other on the wing (Lorenz, 1952). Diebschlag specifically noted that he had himself imposed no punishment of any kind--and indeed, if he had, he would not have made this intriguing observation.

Suppose we wish to study a drug which reduces fear, or is intended to do so. We could make use of these observations in the following way. A pigeon could be trained to avoid a platform, as a result of the very mildly distressing experience of having found inaccessible food there. We should now not even have to expose it to its own imaginary terrors, by trying to retrain it. We could simply administer the drug and see whether the bird now spontaneously and without any alarm visited the forbidden platform. We could expect it to do this if no longer afraid, in light of the original observation that pigeons freely visit unrewarding platforms when hungry. If this very probable prediction were realized, *we should have a method of testing the fear-reducing activity of a drug at any stage of the process inflicting any fear on the animal.* It would be hard to think of a problem which seemed at first sight so totally insoluble, yet we have now considered more than one kind of solution. It is clear, *a fortiori*, that in less exacting investigations the freedom of choice of the experimenter is often very much wider than at first appears. The full use of this freedom is the mark alike of humane and successful experimentation. "Violence is the last refuge of the incompetent" (Asimov, 1953). If we prefer not to seek that refuge, there is perhaps no limit in animal experimentation to the progress of refinement.

[1]A useful systematic discussion of the field.
[2]Besides threat and courtship, a third situation susceptible of similar analysis is that of animals to their young. Analysis here has barely begun (see Russell and Russell, 1957 and in press; Russell, in press, d; and cf. Tinbergen, 1953a, Chapter 3).

[3]I.e. not contaminated with flight or attack components--the word is not used in Bunthorne's sense!