Chapter I

CHEMICAL CO-ORDINATION

§ I

In practically all cellular animals other than sponges visible manifestations of activity involve a receptive surface on which the stimulus operates, a structure specialised for the performance of the appropriate response, and, intervening between these, a mechanism of co-ordination. Co-ordination in animals is of two kinds. Cellular animals in general possess specialised tissues in continuity with both receptor and effector units: this constitutes the nervous system. A large number of animals also possess a special arrangement, the circulatory system, for keeping in motion the fluids which bathe the tissues: the circulatory system provides an avenue through which not only general metabolic changes but active responses of the organism can be regulated by the distribution of specific excitants which are capable of producing local responses of one kind or another. Chemical or endocrine co-ordination is an important aspect of the regulatory processes of the body. Though in some respects more accessible to experimental investigation than the analysis of the nervous function, it is a subject of more recent growth, and one in which our knowledge is at present restricted almost exclusively to vertebrate species. This is partly because research in this field has been motivated in the main by clinical objectives. But there is, it is hoped, sufficient information drawn from materials other than man's nearest of kin to justify a survey from the standpoint of the comparative physiologist.

In embarking upon a study of the rôle of internal secretion in co-ordinating the activities of the organism, it is important to define the precise sense in which the term *internal secretion* will be employed in these pages, since it has been used by some authors in such an indefinite manner as to cover the whole field of intermediate metabolism, a subject which is dealt with in a separate volume of this series. It is the intention of the writer to restrict the term for the purpose of the present discussion to the production of substances which are liberated into the blood stream by the specific activity of a particular structure (endocrine organ), and, when set free in the circulation, are capable of evoking responses in tissues remotely situated from their point of origin. So defined, the term *internal secretion* is in effect synonymous with *hormone*. The latter is sometimes wrongly employed to signify any physiologically active tissue constituent (e.g. the pressor component in pituitary extracts) whether or not it has been proved to have a functional significance or to be liberated into the blood stream. For excitant substances present in animal tissues it is preferable to employ the more general term due to Schafer, *autacoid*. The preparation and investigation of the properties of autacoids is the subject matter of several comprehensive and authoritative works; and information of this kind is of the utmost importance for the furtherance of our knowledge of internal secretion. It is also valuable, now that the subject has progressed so far, to take a retrospective view, and attempt to formulate the extent to which the phenomenon of internal secretion can rightly be regarded as an effective agent in the co-ordination of vital activities. Such treatment must necessarily be orientated with reference to the various modes of activity which the organism displays; and inevitably much matter of a kind which is dealt with in standard works on endocrinology will be omitted from the present account.

Since we are here concerned with the functional significance of internal secretion as part of the mechanism of co-ordination, it will be as well to devote some space at the outset to a critical examination of the type of evidence upon which it is customary to rely for proof of endocrine function. Suggestive indications of the possibility than an organ is an organ of internal secretion in the sense defined above is furnished by a study of the pharmacodynamic properties of tissue extracts and the characteristic disturbances which accompany diseased conditions or operative removal of glandular structures. Investigation of the first type owes its origin to the researches of Oliver and Schafer (1894–5). Information of the second kind dates from before the dawn of medicine to those who introduced the practice of castration—probably in the first place as a religious observance. Though isolated information of this kind is actually the only basis for the customary description of several familiar organs as ductless glands, neither of these criteria can of itself suffice to constitute a rigid proof of endocrine activity.

Thus the fact that extracts of fresh pituitary glands from all classes of land Vertebrates, if suitably prepared, have the specific effect of producing rise of blood pressure in the Mammal and fall of blood pressure in the Bird, is a very good reason for exploring the possible relation of the pituitary to vasomotor regulation. It is not sufficient to justify the inference that such a relation does in fact exist. In pursuing enquiry into the endocrine or supposedly endocrine function of so-called ductless glands the physiologist has no more justification for attributing a teleological significance to every chemical entity in the organism than neo-Darwinian naturalists had for ascribing utility to every member of the body. Apart from this purely formal issue, there are certain technical difficulties to be recognised before sorting out data with reference to autacoid substances. In all tissues after death there are formed by autolysis and putrefaction substances which have pronounced physiological effects. One may say that all commercial preparations contain traces of histamine-like and choline-like compounds. Consequently statements regarding the properties of extracts prepared from an organ should be accepted with caution, unless based upon absolutely fresh material and quantitative comparison with the activity of similarly prepared extracts from other tissues.

Again, experimental removal of organs and the effects of disease can provide valuable indications of their functional importance; but cannot in the absence of collateral evidence suffice to prove that they liberate hormones into the circulation. To infer endocrine activity from this source alone is hardly less unwarranted than to deduce from the manifest consequences of decapitation the conclusion that the head secretes a hormone that maintains the rhythmical contraction of the heart. Nevertheless in one instance this line of argument has been almost universally adopted. With the notable exception of the late Geoffrey Smith nearly every investigator in the field of sex differentiation has referred to internal secretions of the ovary or testis, as if the existence of such secretion were an established fact. What is clearly established is the experience that removal of the ovary or testis prevents the appearance of certain sexual characteristics, as illustrated by the assumption of male plumage, spurs, etc., after spaying in the hen, and inhibition of the growth of the antlers in the castrated male deer, etc. It is also clear that in the Mammal the interstitial tissues are pre-eminently involved. All that can be legitimately inferred from these facts is the conclusion that in some way or other the presence of an ovary or testis determines the way in which sex differentiation proceeds. The development of secondary sex characters—except in the special case where they depend upon sex-linked factors—is the result of differences of metabolism acting upon material of similar genetical constitution. Such differences arise in virtue of the presence of one or other type of gonad. Since we are still quite ignorant as to the nature of the metabolic difference which underlies one or other type of sex differentiation, no economy of hypothesis is effected by assuming that the gonad discharges specific exciting substances into the circulation in preference to the equally plausible alternative that it removes something.

On the basis of his researches on sex transformation in crabs parasitised by *Sacculina*, Geoffrey Smith (1913) pointed out that the blood of the normal female of *Inachus* differs from that of the male in its higher content of certain lipoid constituents absorbed by the ovaries for the formation of the yolk of the egg. These fatty substances form an important part of the food of *Sacculina*, and since normal metabolism involves their production in large quantities as fast as they are used up in yolk formation by the female, the action of the parasite in feminising the male crab would appear to imitate the consequences resulting from the presence of an ovary in stimulating the production of lipoid materials. The parasite absorbs them as fast as they are produced, the only result in the female being the degeneration of the ovary. But in the case of the male the character of the metabolic processes is so transformed that their precursors are produced in quantities comparable with those present in the blood of the normal female, to the somatic organisation of which the crab approximates. It may be doubted whether conclusive proof is brought forward by Geoffrey Smith in support of the proposition that these products of intermediate metabolism are the essential factors in directing somatic differentiation in the direction of the female or male condition. But some such interpretation of the functional rôle of the interstitial tissues is just as acceptable in the present state of knowledge as the sex-hormone hypothesis. Until experiments have been devised and carried out to dispose of one or the other alternative, it is reasonable to preserve an impartial attitude, bearing in mind William of Occam's aphorism *entia non multiplicanda praeter necessitatem*. Having employed this illustration, no further reason need be given for deferring the discussion of the rôle of the gonads in sex differentiation to the volume which deals specifically with that issue. There, for convenience, the endocrine significance of the ovarian follicles of the Mammal will also be set forth. But before proceeding to a consideration of the criteria for ascribing to an organ the function of internal secretion, as we have agreed to define it, there are, concerning the structure of the so-called ductless glands, some few particulars which will be assumed in the following chapters, and which may therefore be referred to most conveniently in this context.

§ II

The structures customarily referred to as ductless glands—pituitary, thyroid, parathyroids, suprarenals and "islets of Langerhans"—are exclusively confined to one phylum of animals, the Chordata, and within that phylum to one large group, the Craniata. It may be assumed that the reader is in a general way familiar with the histological characteristics and developmental origin of these organs. It will suffice therefore to draw attention to such particulars as emerge from recent work.

The practical justification for comparative physiology resides in the fact that some animals provide far more accessible material for the solution of a particular problem than others: given the solution of the problem in a particular species its general applicability is often less difficult to establish. As regards the suprarenal glands the anatomical relations of the constituent tissues are as favourable for experimentation in the Mammal as in any other Craniates; and a discussion of their histology will be reserved for the next chapter. A few remarks on the subject of the thyroid and pituitary glands are however necessary, partly because more is known of the physiology of these organs in the lower Vertebrates, and partly because in the case of the pituitary a good many new morphological facts have come to light during the past few years. A full account of recent work on the pituitary complex will be found in de Beer's monograph (1925). In the past it has been customary to distinguish two epithelial portions, the pars anterior (glandularis) and pars intermedia, derived from the ectoderm (hypophysis), from a portion (pars nervosa) which is non-glandular and derived from the infundibulum of the embryo. An important result of recent work is the recognition of a third glandular portion—the pars tuberalis. In view of the current confusion in nomenclature the following schema from de Beer's paper will be useful to our purpose:

		Adult		*Embryo*	
Pituitary complex	Pituitary body	Anterior lobe (Pars anterior)		from Hypophysis	Epithelial portion
		Pars tuberalis			
		Neuro-intermediate lobe	Pars intermedia		
			Pars nervosa	Primary infundibulum from floor of third ventricle	Neural portion
	Infundibulum				
	Tuber cinereum				

The pars tuberalis, which was first recognised in 1913 by Tilney and more extensively studied by Atwell and his co-workers, is present in all land Vertebrates with the possible exception of snakes and some lizards. In Mammals it lies dorsal to and in front of the pars anterior, set like a collar about the infundibular stalk and covered by the meninges, which fact renders it difficult to clear from the nervous tissue of the stalk itself. Easily recognisable even under low powers of the microscope by reason of its characteristic vesicular structure, the pars tuberalis can be very satisfactorily demonstrated by various staining methods. Though in contact with the pars intermedia in one part (hence formerly called the tongue-shaped process of the pars intermedia) the two portions have an entirely different ontogeny. In Birds the tuberalis is present in all the forms investigated (fowl, duck, pigeon, sparrow), and is specially interesting for reasons stated later. Among Reptiles the pars tuberalis is present in *Sphenodon*, Crocodilia and Chelonia, and is similar to that of Mammalia except that it does not completely invest the infundibular stalk and displays a less pronounced vesicular structure: it does not appear to be present in snakes and some lizards. The Anura present the most arresting feature from the experimental standpoint, since in these Amphibia the tuberalis consists of two lobes anterior to and completely detached from the rest of the gland. In Urodela the pars tuberalis is not as yet separated from the pars anterior. A comparison of the properties of extracts of the anuran gland with those of preparations of the posterior lobe of animals in which the tuberalis is incorporated in the latter may therefore be expected to throw light on the localisation of the active materials.

With regard to the supposed evacuation of the active substances from the pars intermedia into the pars nervosa two points are worthy of mention. It is first to be noticed that while the intermedia is almost devoid of blood vessels the pars nervosa, and especially that portion which borders on the pars intermedia, is well supplied with them in Mammalia, Amphibia and Teleostei. Secondly, though the pars intermedia and nervosa are prone to contain spherical cysts of hyaline material, this is not universal. In a number of cases, notably the cat among Mammalia, the occurrence of hyaline bodies is exceptional, and of fourteen cats the whole glands of which were cut into complete series of sections by de Beer, only one was found to possess these cysts. There are two points in which de Beer's interpretation of the structure of the pituitary in different vertebrate classes differs from that given by previous authors. First, with reference to the elasmobranch pituitary, the so-called inferior lobe has developmental similarities which recall the pars tuberalis of the Tetrapoda; but it is the existence of a pars intermedia and nervosa in the Selachians which concerns us here. From the fact that there is no well-marked lobe consisting of nervous tissue some authors have denied that there exists a differentiated pars nervosa in this group. There is, however, a mass, somewhat small it is true, of neuroglia fibres which leave the floor of the infundibular cavity and ramify in the intermedia. An increase in the quantity of this element would give rise to the condition in the haddock, for example, in which the nervosa is recognised

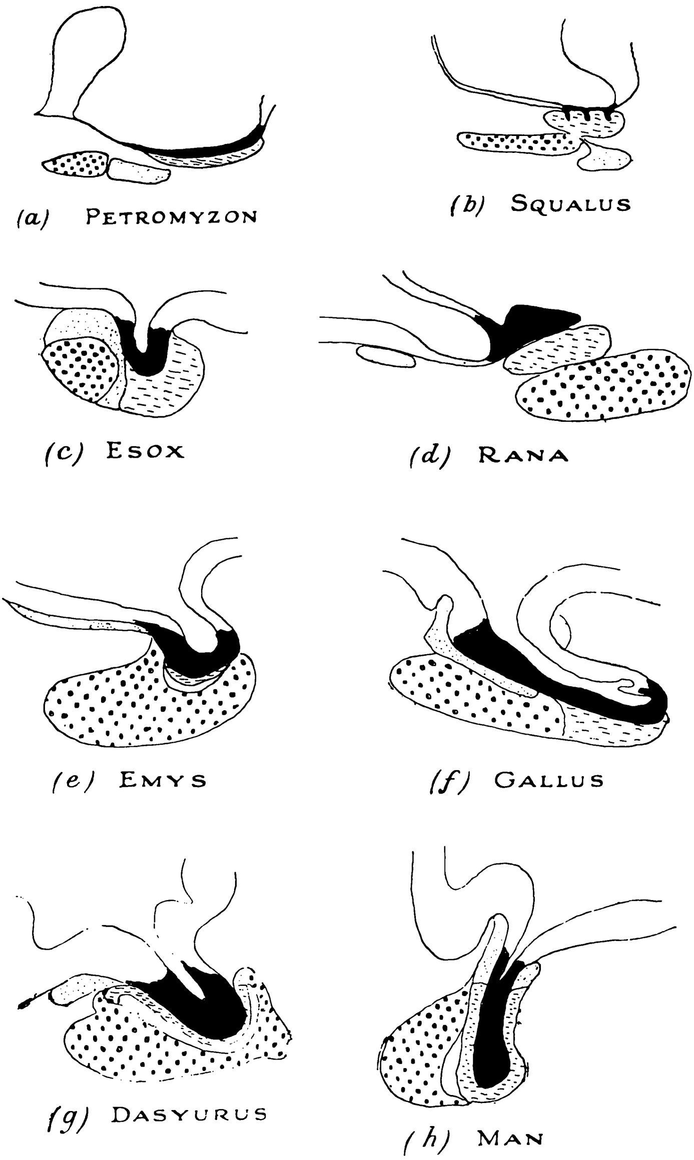

Fig. 1. Diagrammatic representation of the relations of the pituitary in the different groups of Craniates. Large dots, pars anterior; horizontal broken lines, pars intermedia; small dots, pars tuberalis (*übergangsteil*); black, pars nervosa; modified (*c*) and (*e*) from Stendell, (*d*) from Atwell, (*f*) and (*h*) from Tilney, (*g*) from Parker. The anterior end is to the left in each case.

to exist. A second point of some importance is that the pars intermedia, present in all other Craniates from *Petromyzon* to Man, does not seem to be separately differentiated in Birds, where the structure which has been labelled pars intermedia by some other writers appears for the following reasons to be pars tuberalis. It is a thin sheet of tissue encircling the infundibular stalk, but absent from the posterior end of the pars nervosa; it develops from the lateral lobes of the hypophysis; in development the tissue on the posterior side of the hypophyseal cavity is small in account, histologically identical with the developing pars anterior, and consequently, when the cavity becomes obliterated, there is no layer of tissue separating the pars anterior from the pars nervosa; finally, it is highly vascular and vesicular, the vesicles being of an altogether different character from the cysts sometimes found in the pars intermedia. It is well to emphasise one other point of some importance in comparing extracts from the several parts of the mammalian gland for experimental purposes. In some Mammals (pig, sheep, ox) there is a cone of tissue, first described by Wulzen, projecting from the anterior aspect of the pars intermedia. It varies greatly in size and may be larger than the rest of the pars intermedia, from which it differs considerably in histological appearance, resembling more closely the pars anterior with its dense granular eosinophil cells.

These points have been dealt with at some length, because it is quite impossible to regard the pituitary as a single organ from the physiological standpoint, and a clear appreciation of its anatomical complexity must be assumed in later chapters. For experimental purposes it is also valuable to bear in mind a few facts about the development of the gland. The origin of the glandular portion from a hollow ingrowth (Rathke's pouch) on the roof of the stornodalum in Selachians and Amniota is not a universal condition, a circumstance which is propitious to experimental procedure. The hypophysis is initially in Cyclostomes, Teleostei and Amphibia a solid ingrowth anterior to the mouth, so that at a certain stage of development (Fig. 2) it is easily accessible to injury or ablation. In fact the extirpation of the pituitary which has proved a stumbling block to the mammalian physiologist is a comparatively easy matter in Amphibia at all stages of development. In embryos of

Rana pipiens at the 3·5—4 mm. stage, the hypophyseal invagination is readily seen in front of the mouth between the protuberance

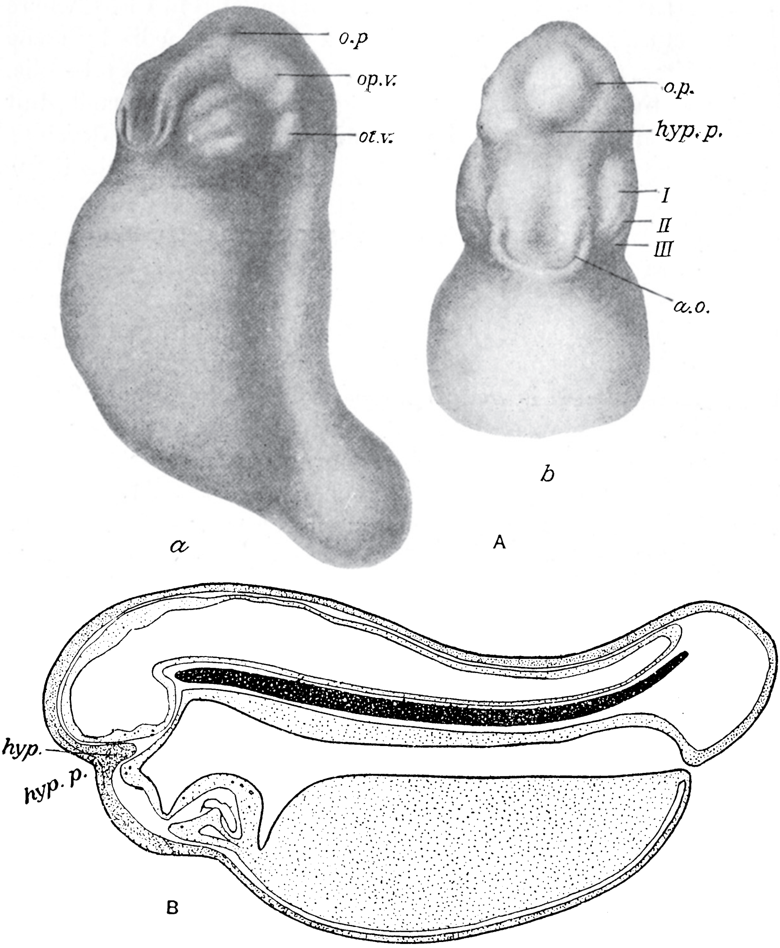

Fig. 2. A. A 4 mm. frog larva (*R. boylei*) showing the surface characteristics at a favourable stage for epithelial hypophysectomy; (*a*) ventrolateral, (*b*) ventrocephalic view. B. A median sagittal section of a frog larva of approximately the same age and size as shown in figure A.

of the fore brain and the stomodaeum which is just forming. The epithelial ingrowth is removed with adjacent epithelium by means of a spear-point needle. Healing takes place within thirty minutes