and not mysteriously through the air, then much of the difficulty may be overcome. Instruction in personal hygiene, mainly the need for clean hands, is worth giving to the family, and parents may be advised to try to prevent their children from indulging in violent exercise, if that is possible, and certainly to put them to bed if they ail even slightly. To offset the irksomeness of these restrictions, it is usually possible to assure the parents that another paralytic case in the family is most unlikely, and that the other children in the family have already had their poliomyelitis. With regard to adults, it is seldom necessary, except in the case of teachers and possibly food handlers, to interfere with their work.

STRESS AND CORTICOTROPHIN

One of the mystifying problems of experimental endocrinology is the manner in which adrenocorticotrophic hormone (A.C.T.H.) is released from the pituitary in response to stress. The rapidity of this response is remarkable, for a stimulus arising in the periphery can cause secretion of A.C.T.H. in a matter of seconds. Much experimental work on this subject has been done, and has been brilliantly reviewed by P. L. Munson and F. N. Briggs[1] in a paper presented at the Laurentian Hormone Conference in 1954. There are now five hypotheses to explain A.C.T.H. release, and all of them are open to objections. The earliest was that of C. N. H. Long,[2] who postulated that adrenaline was secreted in response to stress, and that this acted on the pituitary. However, it has been shown[3] that the "reaction time" of A.C.T.H. secretion after intravenous histamine is extremely short—10 seconds or less—and this also holds for the response to vasopressin, insulin, and ether. On the other hand, adrenaline causes a much more gradual depletion of adrenal ascorbic acid, which is a measure of A.C.T.H. activity, and it seems unlikely that the response to these chemical "stresses" can be mediated through adrenaline. Long never maintained that adrenaline provoked the pituitary to respond to all types of stress, and in fact his group showed[4] that eosinopenia could still be produced in rats subjected to stress after removal of the adrenal medulla, though the response was delayed. He therefore modified his original theory by postulating two stages: an early, autonomic phase due to adrenaline release and a late or metabolic phase due to a reduction in circulating corticoids. This still fails to account for the rapidity of response.

G. Sayers and M. A. Sayers[5] were the first to show that pretreatment with corticoids will inhibit the normal pituitary response to several types of stress. Because of this they suggested that a reduction in circulating corticoids brought about by stress might lead to an increased secretion of A.C.T.H. A similar reciprocal relationship is said to exist between thyroid-stimulating hormone and thyroxine, the level of the latter determining the ability of the pituitary to regulate secretion of its hormone. There are several facts in support of the Sayers's theory—for example, the well-known adrenal atrophy which follows cortisone administration and the adrenal hypertrophy that follows unilateral adrenalectomy. On the other hand, a reduction in circulating corticoids implies that these substances are rapidly utilized or inactivated in stress, and this has not yet been shown. Nor has a fall in blood corticoids been observed; most workers would agree that in fact a rise occurs. Further, Sayers and his co-workers[6] have found that the higher A.C.T.H. secretion in patients with Addison's disease does not return to normal after cortisone treatment, and A.C.T.H. is still secreted by adrenalectomized animals exposed to stress.[7]

The possible role of the hypothalamus in activating the anterior pituitary has been studied by several workers, notably by G. W. Harris[8] in England. It seems more than coincidence that the pituitary lies in close anatomical relationship to the hypothalamus, and the functional relationship of this part of the brain and the posterior pituitary is well established. The hypothesis of Harris, which has been supported and extended by D. M. Hume[9] and others in the U.S.A., is as follows. Stimulation of the hypothalamus by stress results in the transmission of a nervous impulse to the median eminence of the tuber cinereum. Here a "neurohumor" is liberated into the hypophysial portal system of blood vessels and is carried to the anterior pituitary, which it then activates. There is impressive evidence in favour of this view, though the postulated "neurohumor" has not yet been identified. Thus stimulation of certain areas in the hypothalamus, and particularly the median eminence, causes increased secretion of A.C.T.H., while destruction of the same areas prevents the normal pituitary response

[1] Munson, P. L., and Briggs, F. N., *Recent Progr. Hormone Res.*, 1955, **11**, 83.
[2] Long, C. N. H., ibid., 1952, **7**, 75.
[3] Gray, W. D., and Munson, P. L., *Endocrinology*, 1951, **48**, 471.
[4] McDermott, W. V., Fry, E. G., Brobeck, J. R., and Long, C. N. H., *Yale J. Biol. Med.*, 1950, **23**, 52.
[5] Sayers, G., and Sayers, M. A., *Endocrinology*, 1947, **40**, 265.
[6] Sydnor, K. L., Sayers, G., Brown, H., and Tyler, F. H., *J. clin. Endocr.*, 1953, **13**, 891.
[7] —— —— *Endocrinology*, 1954, **55**, 621.
[8] Harris, G. W., *Ciba Foundation Colloquia*, 1952, **4**, 106.
[9] Hume, D. M., ibid., 1952, **4**, 87.
[10] Lynch, J. R., Keller, A. D., Batsel, H. L., Witt, D. M., and Galvin, R. D., *Amer. J. Physiol.*, 1952, **171**, 745.
[11] McDermott, W. V., Fry, E. G., Brobeck, J. R., and Long, C. N. H., *Proc. Soc. exp. Biol. (N.Y.)*, 1950, **73**, 609.
[12] *Adrenal Cortex. Trans. 3rd Conference, Josiah Macy Jr. Foundation, 1951*, p. 71. 1952, New York.
[13] Fortier, C., *Endocrinology*, 1951, **49**, 782.
[14] McCann, S. M., *Amer. J. Physiol.*, 1953, **175**, 13.
[15] Slusher, M. A., and Roberts, S., *Endocrinology*, 1954, **55**, 245.
[16] Guillemin, R., and Rosenberg, B., ibid., 1955, **57**, 599.
[17] McCann, S. M., and Brobeck, J. R., *Proc. Soc. exp. Biol. (N.Y.)*, 1954, **87**, 318.

to stress. Pituitary stalk section, with precautions to prevent revascularization as carried out by Harris, results in adrenal atrophy. Transplantation of the pituitary to sites away from the hypothalamus is also accompanied by adrenal atrophy, whereas these glands maintain their size if the pituitary is placed under the median eminence. Harris's experiments have been criticized on the grounds that the effects of hypothalamic lesions and stalk section may be due to interference with the pituitary blood supply rather than to specific interruption of a hypothalamic–hypophysial pathway. Keller and his associates,[10] for instance, have shown that removal of the ventral hypothalamus in dogs does not abolish the pituitary response (as measured by eosinopenia) to severe operative stress. However, this operation is technically difficult, and stress can cause eosinopenia in the absence of corticoids and A.C.T.H. Nevertheless, ocular transplants of the pituitary will respond to local adrenaline[11] and histamine and to certain types of systemic stress. Hume believes that this phenomenon could be explained by increased sensitivity of a pituitary no longer subject to the inhibitory effect of corticoids. Long has pointed out[12] that Harris's hypothesis would require several different hypothalamic–hypophysial mechanisms to account for secretion of six or more different pituitary hormones.

It seems clear that the type of stress appears to influence the manner in which the pituitary is activated. C. Fortier[13] has put forward a theory of dual control of A.C.T.H. secretion to explain this. He believes that emotional (neurotropic) stress requires an intact hypothalamic–hypophysial pathway, while systemic stresses such as the administration of adrenaline and the carrying out of laparotomy can act by direct stimulation of the pituitary or through some systemic agent. This is not altogether satisfactory, however, because the pituitary response to both adrenaline and surgical trauma can be blocked by hypothalamic lesions[14] and morphine.[1] Strong evidence for participation of the hypothalamus in A.C.T.H. secretion has recently come from another direction. Extracts of posterior hypothalamus are capable of stimulating the production of A.C.T.H. both in the experimental animal[15] and *in vitro*[16]; the active material appears to be a lipid or lipoprotein. The main problem now must be to determine the nature of this "neurohumor," which need not necessarily be identical with the humoral agent that sets off the response to stress. None of the known transmitters—adrenaline, noradrenaline, acetylcholine, or histamine—appears to be responsible. Pitressin has been implicated by a number of workers[17]; and serotonin (5-hydroxytryptamine), which is present in higher concentration in the hypothalamus than in any other part of the brain, is under investigation.

MOLECULAR SHAPE AND ANALGESIA

Morphine is still pre-eminent because its direct action on the brain not only frees the subject from pain but induces calm and wellbeing. Unfortunately it also depresses breathing, may produce a drug addiction, is constipating, and sometimes induces vomiting. Like the majority of drugs, it has a multiplicity of effects, some good, some bad. This is always a challenge to the organic chemist, who will try, by modifying and simplifying the drug's chemical structure, to obtain new products with fewer actions, emphasizing this or that beneficial effect, minimizing one or more of the harmful ones. At the same time he hopes to find something which can be cheaply made by the chemical industry in crystalline purity, without recourse to plant or animal extracts and the complications of biological assay. Two principles underlie such chemistry.

The morphine molecule, a complicated assembly of more than 40 atoms of carbon, hydrogen, oxygen, and nitrogen, has a simple inner order. The atoms are bound together in small groups of recognizably distinct character (such as –OH, $=N.CH_3$, and so on), and from these groups is constructed the ordered molecule. Each group occurs also in many different substances throughout the whole of organic chemistry, always having much the same special chemical and physical properties by which in fact it is recognized, no matter in what particular molecular setting it finds itself. Some of the groups are chemically rather inert. They tend to be on the large size, and are principally straight rods or chains of carbon atoms, or rings of such atoms, especially the six-atom hexagonal ring or benzene ring. Other groups are smaller and chemically active. They will join together if brought near enough in the right circumstances, or in some cases will repel each other.

In the assembly of a molecule the large inert rings and chains have a kind of skeletal function, and carry the small active groups attached here and there, so that they are dispersed on a fixed frame. The kind of frame decides some of the general characteristics of the substance; the individual active attachments decide the detailed pharmacological effects; and the pattern of the active groups in space decides the general pharmacological effect. The chemist removes or replaces individual groups without affecting the basic framework, and he may also obtain similar spatial patterns of active groups by building up on different basic frames. It is rather like some wooden constructional toy where the same set of parts plugged together in different ways may make an aeroplane or an engine, a crane or a house. In fact chemists often make scale models of the molecules of substances which interest them to get a clearer idea of their shape in space and of the interrelationship of their active groups, using wooden spheres and pegs and hexagons.

[1] Braenden, O. J., Eddy, N. B., and Halbach, H., *Bull. Wld Hlth Org.*, 1955, **13**, 937.