anaesthesia throughout the experiment does not mitigate the pituitary-adrenocortical response to the operative stress. (c) That a comparison of the very different changes in the ascorbic acid content in Group IV and the other three groups shows the extent to which the pituitary-adrenocortical response is inhibited by hypothermia.

Further experiments were carried out to determine the degree of responsiveness of the adrenal cortex in hypothermia to varying doses of A.C.T.H. These results are shown in Table II. It will be seen that with a degree of hypothermia of about 20° C. the parenchymatous cells of the adrenal cortex are still sensitive to small doses of A.C.T.H., though there is no linear relationship between dosage and loss of ascorbic acid. Moreover, the response in hypothermia is sluggish when compared with that of hypophysectomized rats at normal temperatures.

Discussion

The rapid fall in the ascorbic acid content in the adrenal glands of animals exposed to various kinds of stress has led to its use for quantitative biological assay of adrenocorticotrophic activity (Sayers *et al.*, 1948). Though the significance of the disappearance of this vitamin is little understood, its loss has been widely recognized as a satisfactory quantitative assay method for A.C.T.H.

The fall in the ascorbic acid concentration in the second adrenal gland in Groups I, II, and III was the expected response of these animals to the various combinations of the stresses imposed by anaesthesia, adrenalectomy, and exposure to cold. When the stresses were imposed on animals that were already hypothermic, as in Group IV, they failed to show any depletion in the ascorbic acid content of the second gland. This implies that at this lowered body temperature the pituitary-adrenocortical mechanism was inhibited. That this inhibition was not due to the effect of the maintained anaesthesia is shown by the response of Group III animals, which were kept anaesthetized throughout the experiment. Nor could it be attributed wholly to lack of sensitivity on the part of the adrenal cortex, for Group V animals showed that with this degree of hypothermia the adrenal cortex still shows some response to small doses of A.C.T.H.

It can be concluded from these findings that at this degree of hypothermia the adeno-hypophysis does not release any appreciable amount of A.C.T.H. in response to the stresses applied. Whether this block is due to an inhibition of certain metabolic activities in the adeno-hypophysis or to the interruption of a neural or neuro-humoral phase in the response mechanism is not clear from the present experiments. The evidence of hypothalamic involvement in the pituitary-adrenocortical response to stress (Porter, 1953) favours the view that, in hypothermia, an inhibition of neural transmission of stress stimuli is mainly responsible for this block. The study of the effects of hypothermia on the stress response may be a useful guide to the further understanding of the mechanism involved.

Summary

Evidence is given to show that in hypothermic rats the hypothalamic-pituitary mechanism leading to the release of A.C.T.H. in response to stress stimuli is inhibited. The adrenal cortex in such chilled animals, however, remains responsive to the intravenous injection of small doses of A.C.T.H.

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A SIMPLE METHOD OF RAISING AND LOWERING BODY TEMPERATURE

BY

H. H. KHALIL, M.B.

AND

R. C. MacKEITH, D.M., F.R.C.P.

(From the Departments of Pathology and Child Health, Guy's Hospital, London)

While studying the effects of stress in hypothermic rats it was noted that at a body temperature of 20° C. the pituitary response was inhibited and that of the adrenal cortex was much reduced (Khalil, 1954). With these small animals changes in body temperature could be effected readily; when dogs and rabbits have been made hypothermic, rewarming by the external application of heat takes much longer than with rats, and this delay may have contributed to the death of some of the animals. The introduction of warm water into the stomach could provide a simple and rapid method for supplying heat to the body, since the stomach wall is highly vascularized and lies close to the aorta, vena cava, portal vein, and other large vessels. Conversely, by using cold water a marked degree of hypothermia can be attained.

Since repeated changes of cold or warm water are needed to effect the desired temperature changes, the water is introduced through a tube which joins a rubber balloon lying in the lumen of the stomach. By this procedure the water remains "external" to the body and any loss of electrolytes by gastric lavage or excessive absorption of water is avoided.

The apparatus used consisted of a thin "portex" plastic tube with a finger-stall, which on inflation could readily hold 250 ml., tied securely to one end. The other end was attached to a two-way tap connected with a 50-ml. syringe and with a rubber inlet tube from the warm or cold water to be used. The temperature of the former is about 40° C. and of the latter about 4° C. The irrigation was carried out once every five minutes, each change of water remaining in the balloon for about three minutes. The method was employed for rabbits and was effective in lowering the rectal temperature to about 25° C. in two hours and to 20° C. in three hours and in raising it to normal again in about four hours. The heart rate was slowed from 240 to 60 beats per minute. This work will be reported more fully later.

At this stage an opportunity arose of using this method for cooling a 16-months-old child with hyperpyrexia who had not responded to the usual methods of cooling.

Case History

A boy aged 16 months was admitted to hospital on June 29, 1954, with pneumonia, which resolved with treatment. There was a family history of fits, and the boy had had severe fits at 10 months while teething. On the first and second day after admission he had fits and was left with a right hemiparesis and regression in general behaviour to that of a 10-months-old child, although he was alert and active. On July 15 he was transferred to Guy's Hospital, and on July 16 an arteriogram was done which showed slight shift of cerebral vessels to the left. On the morning of July 20 he had a temperature of 104° F. (40° C.); no abnormality was found in the throat, ears, lungs, and urine. At 1 p.m. he was stuporous and very ill, with cold skin

and a rectal temperature of 105° F. (40.6° C.). Despite repeated cold applications for five hours the temperature did not fall below 103.5° F. (39.7° C.).

The intragastric balloon devised for rabbits was passed with ease. After 150 ml. of water at 32–39° F. (0–4° C.) had been introduced slowly over five minutes, the rectal temperature began to fall (see Chart). Some extrasystoles were noted. After staying two minutes in the stomach, the 150 ml. was withdrawn; its temperature was about 80° F. (26.7° C.). Between the 11th and 13th minute after

Graphical representation of cooling the child on the first occasion.

starting cooling a further 200 ml. of ice-cold water was injected, extrasystoles being noted again towards the end of the injection. After one and a half minutes this was withdrawn. Between the 17th and 20th minute 200 ml. of water (making a total of 550 ml.) was injected. At the 21st minute the temperature rose to 102.6° F. (39.3° C.). During the next 26 minutes, five further changes of 200 ml. each were given. Despite this faster rate of exchanges no further extrasystoles were detected either by auscultation or by intermittent E.C.G. records, even immediately after filling the stomach with ice-cold water. At the 29th minute the temperature was 102.4° F. (39.1° C.), and the skin of the body felt warmer.

At the 30th minute the patient began to awake from his stupor and to protest. Salivation was noted from this time on. At the 32nd minute he began shivering. By the 37th minute the body, arms, and legs felt warm (except over the stomach, where the skin felt icy cold). At the 50th minute the temperature was 100.6° F. (38.1° C.); three further lots of 200 ml. of water were injected and withdrawn during the next 18 minutes without further fall in temperature. At the 68th minute the child was very lively and the skin felt normally warm. His general condition was greatly improved and the tube was withdrawn. A total of 2,150 ml. of water had been introduced and withdrawn.

About four hours after stopping the intragastric cooling the rectal temperature had risen again to 103.6° F. (39.8° C.) and the boy had relapsed into stupor with cold, pale, greyish skin of the trunk and limbs. The tube and rubber bag were reintroduced. During the next hour twelve changes each of 200 ml. of cold water at 32–39° F. (0–4° C.) were made. As a result the body temperature fell from 103.6° F. (39.8° C.) to 100.6° F. (38.1° C.). By the 32nd minute he had woken sufficiently to cry and move about; satisfactory improvement in circulation and body temperature took longer on this occasion, for it was not observed until an hour after cooling had been started. The tube was removed at the 65th minute. At the 75th minute the child was taking milk by mouth with good appetite. He has kept well and has remained apyrexial.

Discussion

In experimental work on hypothermia, difficulties arise during the rewarming stage after a marked lowering of the body temperature has been produced. As has been learnt in treating men exposed to severe cold, warming by external

application of heat to the body surface may have serious disadvantages. The warmed peripheral tissues may increase their metabolic demands before the blood supply is adequate. Moreover, if the capillary bed of the skin opens before the general circulation has improved, there will be a fall in blood pressure. Rewarming by the intragastric route avoids these troubles. Furthermore, the skin circulation of the hypothermic animal, including man, is so reduced that little heat may be conveyed from the warmed skin. By internal warming, heat is applied to the vascular gastric mucosa and

to the great vessels close to the stomach; their circulation is never stagnant. This method has further theoretical advantages which may prove to be important. It seemed to one of us (H. H. K.) that if the liver could be warmed first, then heat would also be gained from the various metabolic activities of this important organ. Furthermore, an "active" liver would be better able to meet the increasing metabolic demands of the body during warming.

As regards cooling, much of the above discussion applies. The method has proved practicable for rabbits and for a child. It has the advantages over arteriovenous and venous methods that it does not

involve opening any blood vessels or cooling the blood to such low temperatures that the dissociation of its oxyhaemoglobin becomes seriously impaired (Barcroft and King, 1909–10).

The success of the intragastric method in the case of this child is an example of the possible applications in clinical medicine. Warming is needed for patients suffering from exposure to cold or occasionally in refrigeration plants. On the other hand, cooling may be required for patients suffering from heat stroke or hyperpyrexia in the course of infective and cerebral diseases. A marked degree of hypothermia is also indicated on occasions in operative surgery.

Although the application of the method to a child was successful, some modifications of the procedure used suggest themselves. (1) Salivation was profuse as revival began and atropine might be given with advantage. (2) Extrasystoles were observed in the early stages of cooling. These might be avoided if the first changes of water were not ice cold. They, however, did not continue, although the rate of introduction of fresh changes of cold water was increased. (3) By fitting two catheters into the intragastric balloon further advantages could accrue. The reduction of temperature of the intragastric contents could be made gradual; this could be easily controlled if the balloon were fitted with a thermocouple. The continuous flow achieved by using two catheters would make a more rapid exchange of water possible. This improvement would probably increase considerably the rate of temperature change, a step which might be necessary in adults.

An approximate calculation may be made of the exchange of heat in the child. Though the water introduced was drawn from a reservoir containing melting ice, it is probable that in passing through the tubing and syringe held in the operator's hand it was slightly warmed. It may be assumed that it was at about 4° C. on entering the stomach. In the first cooling of the child the temperature on withdrawal was as follows:

150 ml. ..	80° F. (26.7° C.)	200 ml. ..	60° F. (15.6° C.)
200 ml. ..	70° F. (21.1° C.)	200 ml. ..	60° F. (15.6° C.)
200 ml. ..	68° F. (20.0° C.)	200 ml. ..	66° F. (18.9° C.)
200 ml. ..	64° F. (17.8° C.)	200 ml. ..	62° F. (16.7° C.)
200 ml. ..	64° F. (17.8° C.)	200 ml. ..	65° F. (18.3° C.)
200 ml. ..	65° F. (18.3° C.)		

Warming 2,150 ml. of water from 4° C. to a mean temperature of 19° C. would require about 32 large calories.

The child's weight was 12 kg. The fall in body temperature was 1.6° C., from 103.4° F. (39.7° C.) to 100.6° F. (38.1° C.). Assuming the specific heat of body tissues to be 1, then in this cooling the body would give up 20 large calories. The difference, 12 large calories, probably represents much of the endogenous heat produced and removed during the period of cooling.

Summary

A method of raising and lowering the body temperature in animals and man by the introduction of changes of water into an intragastric bag is described. It has possible applications in the treatment of excessively high and low body temperatures and also in the management of hypothermia in operative surgery.

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JUSTIFICATION FOR APPENDICECTOMY IN CHRONIC APPENDICITIS

BY

IAIN McLENNAN, F.R.C.S.Ed., F.R.F.P.S.

Surgeon, Out-patient Department, Glasgow Royal Infirmary

AND

J. KENNEDY WATT, F.R.C.S., F.R.F.P.S.

Surgical Registrar, Glasgow Royal Infirmary

The very existence of chronic appendicitis is often a subject of controversy, yet appendicectomy for this condition is one of the most commonly performed surgical operations. Is there any justification for removing the appendix of a young man or woman complaining of pain in the right iliac fossa? An investigation of a large series of cases was undertaken in an attempt to elucidate whether operation had been justified by results.

When appendicectomy is performed in patients suffering from recurrent attacks of pain in the right iliac fossa there is usually very little correlation between clinical, operative, and pathological findings. The removal of an apparently normal appendix may relieve the patient of all symptoms, yet little or no relief may be obtained from the excision of a fibrosed and adherent organ.

The difficulty of assessing the significance of pathological changes in the appendix is well illustrated by the findings of Shelley (1937). He found that 63% of the appendixes removed incidentally in the course of other operations showed inflammatory changes, and that 72% of the appendixes removed for chronic appendicitis showed similar changes, the other 28% being normal microscopically. Further, in an inquiry into the clinical aspects of the condition, he found (1938) that of those patients whose appendixes showed microscopical evidence of disease, 89% could be regarded as cured, but where the appendix was microscopically normal the cure rate was as high as 80%. It would therefore seem that an appendix showing pathological changes is only slightly more likely to be a cause of symptoms than an apparently normal one. It seems equally clear that the presence of inflammatory changes is no guarantee that the symptoms are due to these. Accordingly,

fibrosis and adhesions may be more indicative of previous appendicitis than of present symptoms.

The part played by faecaliths in acute appendicitis seems fairly well established (Shattock, 1916), but their importance in chronic appendicitis is less certain. That their presence may be responsible for attacks of appendicular colic is generally accepted, but the frequency of such occurrence is in doubt, as is the significance of faecaliths found at operation. The belief that they do have some importance is supported by Shelley's (1937) findings that where faecaliths formed the only pathological finding the cure rate of appendicectomy was 85%, compared with 74% for appendixes showing no apparent abnormality.

Chronic appendicitis has long been incriminated as a cause of pylorospasm and dyspepsia, and there is no doubt that many cases of dyspepsia are clinically improved by appendicectomy. Whether this is a case of cause and effect or merely the result of the rest enforced by convalescence from the operation is a matter for discussion. That the early benefit conferred on many cases of undiagnosed dyspepsia is considerable and misleading is well exemplified by an article on five such cases written by Moynihan in 1910. The correspondence evoked by this article is illuminating, and a possible result was to induce a spate of appendicectomies in the treatment of dyspepsia which may not have completely subsided yet. Confusion regarding the interrelation of stomach, duodenum, and appendix is also shown in an article by Braithwaite (1942), in which he states that duodenal ulcer is often mimicked by chronic appendicitis and that haematemesis occurs in about 4% of cases of the latter disease. Such a misconception possibly arises from overreliance on the accuracy of radiological diagnosis, which, although reliable in the demonstration of chronic peptic ulcers, is fallible in the elucidation of recurrent minor ulceration.

Radiological examination of cases of chronic appendicitis is not helpful, and generally no specific evidence of disease is procurable. It may, on occasion, enable one to relate tenderness accurately to the appendix, but the main value of barium examinations lies in the exclusion of other pathological conditions of the gastro-intestinal tract.

Present Investigation

In view of certain doubts about the existence and importance of chronic appendicitis, the present investigation was undertaken. All patients operated on for chronic appendicitis in one unit of the Glasgow Royal Infirmary from 1946 to 1950 inclusive were contacted so far as was possible and interviewed. The years 1945 and earlier have not been included, as during the war these cases were dealt with mainly by the hospitals of the Emergency Medical Service, and the years subsequent to 1950 have been excluded to allow an adequate interval between operation and interview. In all, 429 females and 134 males were available for study and 316 females and 97 males were traced, a follow-up of 73.3%. Of those traced, the majority (65%) were personally interviewed and examined by us, and the remainder replied to a questionnaire.

A certain degree of selection of the cases submitted to operation is bound to have occurred, since these cases were admitted via the out-patient department, but the selection was not unduly rigorous and patients complaining of persistent and recurring pain were usually admitted for operation. The basis of this inquiry, therefore, lies in the assumption that those in whom the diagnosis had been correct would, after operation, remain free from pain; and, conversely, if a similar pain persisted after appendicectomy the diagnosis had been wrong. In many of the latter group