ness. The period between consumption of milk and onset of symptoms was twelve to twenty-four hours in those cases where this could be determined.

Additional Inquiries

On January 11, when the cause of the outbreak first became clear, all the medical practitioners in the town were informed of the facts and were asked for information as to any further cases which might come to their knowledge. Inquiries were also addressed to the larger local works.

Investigations as to the food and milk supply were undertaken in all cases reported—a comparatively small number—but it was not possible to determine that any further supply of milk or other article of food had been infected.

Precautionary Measures

In view of general statements from medical practitioners to the effect that a large number of sporadic cases with similar symptoms had occurred recently in the town, it was at first considered a possibility that other milk supplies might have become infected, and therefore consumers were advised through the Press to boil all their milk. When further investigation failed to reveal any common source of cases other than the one already known it was decided that this precaution might be discontinued.

Comments

Dysentery, as is well known, has been widely prevalent throughout the country in recent months, and this has generally been due to the Sonne bacillus. During the weeks ending January 8, 15, 22, and 29 the number of cases notified in England and Wales was 256, 256, 291, and 250, respectively. Dr. A. A. Jubb of the Ministry of Health in a communication states as follows:

"It is a reasonable conclusion that this outbreak was milk-borne, although the mode of infection of the milk has eluded investigation. The detection of the Sonne bacillus in milk has not previously been reported, and the occurrence is therefore of importance for our records.

"You will be interested to know that we have received several reports of very full and even laborious inquiries made by medical officers of health into the origins of outbreaks of dysentery during the recent prevalence, but so far nothing tangible has resulted, except that in two instances an article of food was found to be infected with Sonne bacilli. In a few institutional outbreaks, however, it has been possible, owing to the circumstances of a closed community, to trace with a fair degree of certainty the course of a Sonne infection through an article of food, but bacteriological confirmation has been lacking."

In reviewing the course of the outbreak it is easy to see that several mistakes were made. Some of these were perhaps inevitable at the early part of the investigations, when knowledge was incomplete, and some, with the experience gained, might be avoided in a future outbreak. In the first place, at the outset it would have been wiser to suspect an illness of human origin rather than some toxic condition of the milk as the result of possible illness of the cows, which was at the first in my mind. There was at the time, however, nothing to point specially to dysentery, nor did I realize that this illness had so short an incubation period. Secondly, the fact that nearly all the cases would have remained undiscovered if a house-to-house inquiry among all consumers had not been made shows that it is useless to rely upon a statement from the milkman as to any illness among his customers, even if

this had been widespread. In fact, had it not been for the chance information received from a neighbouring office the outbreak might have been undetected, though probably this would have made no difference to its course. Again, it is difficult to say whether it was sound judgment to determine not to stop the milk supply on the evidence available at the time and before definite infection of the milk was known. I should always hesitate to take this action unless there was good evidence that milk had caused, and was continuing to cause or to be likely to cause, serious illness among consumers. As it still appears probable that the retailer himself became infected after the onset of the outbreak, I am of the opinion that there was no reason to prohibit him from taking part in handling milk or vessels at an earlier stage than was in fact done.

Summary

1. An outbreak of Sonne dysentery due to drinking milk is described.
2. Fifty-nine out of 106 households, or ninety-six among 224 individuals (estimated), were affected.
3. The incubation period was usually twelve to twenty-four hours.
4. Symptoms as a rule lasted twelve to thirty-six hours.
5. Sonne dysentery bacilli were isolated from faeces of some of the patients and from the milk itself.
6. The actual source of infection of the milk remains untraced.

THE GONADOTROPIC ACTIVITY OF THE ANTERIOR PITUITARY GLAND IN RELATION TO INCREASED INTRACRANIAL PRESSURE

BY

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It is known clinically that a considerable increase in the intracranial pressure, in cases of cerebral tumour, may lead to irregular and even complete cessation of menstruation. This effect is presumed to be due to mechanical compression of the pituitary gland. An investigation of a single case of increased intracranial pressure during pregnancy showed that there was a notable decrease in the hormone content of the placenta and urine (Henderson and Robson, 1936). This result led us to investigate the effect of increased pressure on the amount of gonadotropic hormone in the pituitary of men and non-pregnant women. The results obtained relative to increased pressure are inconclusive, but interesting observations have been made on the pituitaries from cases with normal intracranial pressure, which served as controls to the above series.

Material and Methods

In all, 109 human pituitary glands were assayed for gonadotropic activity. Fifty-seven of the glands were from patients (twenty-eight men and twenty-nine women) with normal intracranial pressure who died at the National Hospital, Queen Square, from a variety of general and neurological diseases other than acute infections. The

remaining fifty-two patients (twenty-eight men and twenty-four women) all died from the effects of cerebral tumours (without operation) which had produced an increased intracranial pressure of varying duration. The intracranial pressure in the majority of them, as measured by lumbar puncture, was 250 to 400 mm. of water, the normal pressure being 100 to 150 mm.

The pituitary gland was removed at necropsy, and the anterior lobe dissected, weighed, desiccated in acetone for forty-eight hours, and subsequently dried in a current of hot air. No attempt was made to prepare a purified extract containing the gonadotropic hormone. For assay the acetone-dried tissue was separated from the sheath of connective tissue, ground to a fine powder, and suspended in water made slightly alkaline with NaOH. Nearly all of the tissue goes into solution under these conditions. The extract was then adjusted to pH 7.5 and tested on immature rats. Groups of ten rats, 40 to 50 grammes in body weight, were injected subcutaneously once daily for five days, and killed twenty-four hours after the last injection. The ovaries and uterus were dissected, fixed in Bouin's fluid overnight, and weighed afterwards from 70 per cent. alcohol. In order to have a standard by reference to which the individual pituitaries could be compared, a mixed sample of acetone-desiccated anterior pituitary powder (AP 47) from nine men and five women whose ages ranged from 50 to 65 years was made. The dry powder from these fourteen glands had a total weight of 0.82 gramme.

A dose-response curve was then constructed for the capacity of this preparation to stimulate the ovaries of the immature rat. This curve is shown in Fig. 1 of the article by Boycott and Rowlands at page 1097 of this issue. From the response evoked by this mixed powder it was found that there was sufficient activity in most pituitaries to carry out individual assays, using a group of five rats, by the above method. There was not, however, enough material in the pituitary of very young children to assay each one separately, so a number of these glands were grouped according to age and assayed together. The amount of each pituitary required to give a significant response, measured by ovary weight, was then compared with the amount of the standard preparation necessary to give the same response. From this comparison the activity of each gland was expressed as a percentage of that of the standard.

Gonadotropic Activity of the Human Pituitary under Conditions of Normal Intracranial Pressure

The type of response produced in the ovary of the immature rat by human pituitary extract is qualitatively similar to that produced by extracts, such as those from horse pituitary and pregnant mare serum, which contain a highly effective gonadotropic complex. It contrasts strongly with that produced by extracts of human pregnancy urine and human pregnancy serum (Boycott and Rowlands, page 1097 of this issue), which are capable of evoking only a limited response of the rat ovary. The gonadotropic activity of the normal adult human pituitary, when tested on immature rats, is also quantitatively much greater than that of any other species so far examined. Hill (1935) found a pronounced species difference in the gonadotropic activity of the pituitary, tested by the production of ovulation in oestrous rabbits, and extracts of horse pituitary proved to be the most active of the species which he examined. One human pituitary from a man aged 64, assayed by Hill, showed much less activity than

the pituitary of most of the domestic animals used in experimental work. The activity of the pituitary of men of this age, however, when tested by the increase in weight of the ovary of the immature rat, as in the experiments here recorded, is about ten times as great as that of any other species so far examined.

From Fig. 1 it is seen that in both sexes the content of gonadotropic hormone in the pituitary increases with age. During early childhood the pituitary contains only small amounts of the hormone.

FIG. 1.—The gonadotropic activity of the pituitary of men and women with normal intracranial pressure. The women are classified with regard to the occurrence of menopause. Activity is expressed as a percentage of that of the standard preparation.

The activity of a group of seven pituitaries from female children up to 1 year was 14 per cent. of that of the material used as a basis of comparison, whereas that of a similar group of pituitaries from males of the same age was only 6 per cent., and that of another group of pituitaries from males of 1 to 2 years was only 5 per cent. The data from this age to that of 20 years, and again from the ages of 25 to 35, are unfortunately very scanty, but they indicate a gradual increase in the content of gonadotropic hormone in the pituitary, the amount being greater in women than in men. Up to the age of 50 years, in both sexes, with two exceptions, the amount of gonadotropic hormone in the pituitary does not exceed 50 per cent. of that in the standard material. One of the two exceptions, a pituitary with an activity of 75 per cent., was from a woman aged 22 years from whom no menstrual history could be obtained; the second, a pituitary with an activity of 85 per cent., was from a woman aged 44 years in whom menstruation had ceased about one year previously.

With the appearance of the menopause there is an abrupt increase in the gonadotropic activity of the female pituitary, which persists throughout the remainder of life. All the pituitaries examined, from women past the menopause, showed a gonadotropic activity between 80 per cent. and 354 per cent. that of the standard, with the exception of a pituitary with an activity of only 38 per cent. from a woman 53 years of age. There is therefore, after puberty, an inverse relation between sexual activity, as indicated by the occurrence of menstruation, and the amount of gonadotropic hormone in the pituitary.

There does not seem to be the same rapid increase in the amount of gonadotropic hormone in the pituitary of the male after 50 years of age. The gradual increase that was observed up to 50 years is maintained, but not until an age of about 70 is there any evidence of a sharp rise in the content of gonadotropic hormone. Of the six pituitaries from men of 70 years of age or more that were examined, only two, at ages of 71 and 72 years respectively, showed a gonadotropic value greater than that of the standard preparation. One pituitary from a man of 89 years gave a value only 48 per cent. of that of the standard.

Gonadotropic Activity of the Human Pituitary under Conditions of Increased Intracranial Pressure

The gonadotropic activity of the pituitary associated with normal and with increased intracranial pressure is shown in Figs. 2 and 3, for the women and men respectively.

FIG. 2.—The gonadotropic activity of the pituitary of women with normal and with increased intracranial pressure

tively. Increased intracranial pressure, in either sex, does not appear to alter the amount of gonadotropic hormone in the pituitary, although in both men and women with

high intracranial pressure the hormone content of the gland seems to be more variable than normally at the ages of 30 to 45 years. Since this variation might be due to loss of sexual function a comparison was made

FIG. 3.—The gonadotropic activity of the pituitary of men with normal and with increased intracranial pressure

between the degree of activity of the pituitary of women and the occurrence of menstrual dysfunction, and it seems that in some cases of increased pressure there is a premature rise in gonadotropic activity, similar to that which occurs shortly after the menopause (Fig. 2). There is, however, no regular correlation of this nature.

The degree of activity of the pituitary was also considered in relation to the duration of the increased intracranial pressure. When the sella turcica is normal in size it is probable that the increased pressure is due to a rapidly growing tumour and has been of short duration, whereas an enlarged and atrophic sella the floor of which is partly or completely absorbed is indicative of chronic high pressure from a slowly growing tumour.

In Fig. 3 is shown the effect of increased intracranial pressure of long duration (up to six years) on the gonadotropic activity of the pituitary of men. In such cases it is seen that the activity of the gland is normal, except in one case with an unusually high and in another with an unusually low hormone content.

Discussion

From the results given above it is seen that in man a relationship occurs between the content of the gonadotropic hormone in the anterior pituitary gland and the functional activity of the reproductive organs. In both sexes, from birth to the decline of sexual function, there is a gradual increase in the hormone content of the gland. At the menopause, however, there is a great increase in the amount of gonadotropic hormone in the pituitary of women, but in men this increase does not occur before senility, when it is probably associated with the decline of testicular activity. The significance of this increase in the amount of hormone in the pituitary when gonadal activity declines is difficult to explain. It seems certain that lack of gonadotropic hormone is not the cause of the loss of ovarian and testicular function. More

likely the decline of sexual function may be attributed to the gonads becoming insensitive to stimulation, and the greater hormone content of the pituitary at this time may be due to increased secretion by the gland in response to the insensitivity of the gonad. It is unlikely that the increased activity of the pituitary is due to accumulation of the hormone in the gland, through its failure to be released into the circulation, since after the menopause a gonadotropic hormone which is probably of pituitary origin can be extracted in appreciable quantities from the female urine. Possibly the increased amount of hormone in the pituitary and in the urine after the menopause is due simply to the failure of the gonad to utilize existing supplies.

Since there is a great increase in the activity of the pituitary after the natural decline of reproductive function it might be expected that it would occur if the normal activity of the reproductive organs is otherwise impaired. Such impairment is sometimes seen in cases of cerebral tumour with an increased intracranial pressure, which may disturb or even suppress the menstrual rhythm. The results obtained on the pituitaries of such patients were rather inconclusive, although the activity of some of the glands tended to be greater than normal. It is not known whether this is due primarily to a disturbance of ovarian function or to the direct effect of the increased pressure on the pituitary. The amenorrhoea in all the cases was of short duration, so that no comparison could be made between the duration of menstrual dysfunction and the activity of the pituitary.

From the action of human pituitary tissue on the ovary of the normal immature rat it cannot be decided whether there is a change, at any stage of life, in the qualitative nature of the gonadotropic complex of the human pituitary. It is hoped that experiments at present being made, in conjunction with Dr. R. L. Noble, on hypophysectomized rats will throw light on this question.

The experiments of Saxton and Loeb (1937), in which human anterior pituitary tissue was implanted into immature guinea-pigs, suggested that during childhood the pituitary contains follicle-stimulating hormone and only small amounts of luteinizing hormone, but that later in life there is an increase in the amount of the latter substance in the pituitary of individuals of either sex during or after the period of sexual activity. It is possible that the discrepancy between these observations and those recorded above may be explained by reference to the different test animals used.

Summary

After being desiccated in acetone 109 human pituitary glands were assayed individually on groups of immature rats for gonadotropic activity. Fifty-two of the glands were from patients with increased intracranial pressure due to cerebral tumours, while the remaining fifty-seven glands, from cases with normal intracranial pressure, served as controls. The activity of each gland was expressed as a percentage of that of a mixed sample of human pituitaries which was used as a standard preparation.

The control series showed that the gonadotropic activity of the pituitary varies with age. During early childhood the amount of hormone in the gland is small, but it increases slowly to the end of the period of sexual activity. In women at the menopause there is a sudden rise in the activity of the pituitary, but in men a corresponding increase does not occur until about the seventieth year. The significance of this is briefly discussed.

The amount of gonadotropic hormone in the pituitary of patients with increased intracranial pressure tends to be more variable than in normal subjects. Several of the women showed menstrual dysfunction, and there was a suggestion of a premature rise in the amount of gonadotropic hormone in their pituitaries. There appears, however, to be no relation between gonadotropic activity and the duration of the increased pressure.

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THE BIOLOGICAL NATURE AND QUANTITATIVE VARIATION OF THE GONADOTROPIC ACTIVITY OF PREGNANT WOMEN'S SERUM

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It is already known that gonadotropic material extracted from pituitary tissue differs in its biological reactions from that of human urine of pregnancy. When tested in immature rats, pituitary extracts cause an almost unlimited increase in ovary weight, whereas urinary extracts, in which the gonadotropic material is probably of placental origin, cause only a strictly limited response. Also, in hypophysectomized immature rats pituitary extracts will produce follicular growth and luteinization, leading to increase in ovary weight. Urinary extracts in similar animals give little, if any, increase in ovary weight, although considerable luteinization takes place. These and other experiments suggest the existence of two gonadotropic factors—that is, follicle-stimulating hormone and luteinizing hormone, only the latter being present in extracts of urine of pregnancy.

The investigation described below was made to ascertain some of the biological properties of the gonadotropic material which can be extracted from human blood serum during pregnancy, and to compare it with gonadotropic material from other sources, particularly with highly purified extracts from pregnant mare serum.

Quantitative estimations of the amount of gonadotropic substance present in the blood of pregnant women have been made by Evans, Kohls, and Wonder (1937), who found that its concentration was at a maximum between the thirtieth and the forty-sixth day (pregnancy being dated from the beginning of the first missed menstrual period), at the same time as the gonadotropic substance in the urine reached its maximum. On the other hand, Kennedy (1933) found in a very wide range of cases that as pregnancy advances there is a gradual increase in the concentration of the substance in the blood. The present work shows that there is a high peak in the concentration

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