OESTRIN AND PROGESTIN IN SECONDARY AMENORRHOEA

BY

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In 1933 Kaufmann^{1,2} described his treatment of forty cases of amenorrhoea, in all of which three normal periods had followed injections of oestrin and progestin. The technique he adopted was to give 250,000 international units of oestrin every three days for five doses, followed by three days' rest, and then thirty-five rabbit units of progestin distributed over five consecutive days, the total amount of oestrin for a course of treatment being one and a quarter million international units, or 50,000 rat units.

If too much oestrin was used Kaufmann found that cystic hyperplasia of the endometrium resulted, this condition being analogous to that found in metropathia haemorrhagica, but it required the administration of over five million international units before this happened.

A rat unit is equivalent to five mouse units and to twenty-five international units, and is described as the minimum quantity of ketahydroxy-oestrin required to produce a cell picture of oestrus in the vaginal smear of ovariectomized rats; 50,000 international units are equivalent to 1 mg. of the dihydro-oestrin; and 26.7 mg. of the crystalline benzoate are needed to produce a single period. The dihydro-oestrin is five times the strength of the ketohydroxy-oestrin.

By this technique Kaufmann was able not only to cure secondary amenorrhoea but also to produce the normal physiological changes in the endometrium of a castrated woman. In cases where the amenorrhoea was due to hypoplasia of the genitalia, heavier doses of oestrin were necessary, and in one case he recorded that over eight and a half million units were given in six months without any demonstrable result. When the dose was increased to one million units weekly the growth started, and after a few weeks the uterus was the size of a normal woman's.

Bishop, Cook, and Hampson³ at Guy's Hospital, using a similar technique, reported almost identical results. Their *modus operandi* differed but slightly in that they gave their injections of 250,000 international units on the first, fourth, eighth, eleventh, and fifteenth days, but on the nineteenth, twentieth, twenty-first, twenty-second, and twenty-third days, they gave only one rabbit unit of progestin as compared with the seven units given by Kaufmann. This latter figure they considered to be too much, and as they have obtained comparable results using one-seventh of the dose they are presumably right.

American Results

The whole question of dosage is of great importance, and there seems to be a considerable variation in the estimates of different authors. The only serious attempt to discover the relation of oestrin administered to clinical result obtained was made in America by Werner and Collier.⁴ They found that injections of theelin in castrated young women whose uteri were intact produced endometrial hyperplasia, with uterine bleeding in some cases, and activity of the breasts and alleviation of the subjective symptoms in all cases. Moreover, the libido was increased in four out of five patients, and those in whom no uterine bleeding occurred had the usual psychical phenomena and discomforts which accompany the menses. These observations were the result of random injections of theelin, and in order to estimate the correct dosage necessary to duplicate these results Werner and Collier did the following experiment.

They selected eight women who had been castrated but whose uteri were intact. All had atrophic breast changes, markedly decreased or absent vaginal mucous secretion, and

all complained of the usual castration symptoms. Four curettings were done on each patient; the first, before the injections were started, and then one at the end of every twenty-eight-day period for three months. All the patients were treated for thirteen weeks, and the doses of theelin varied from massive doses down to 100 rat units every other day. Consistent changes were noted in the breasts, cervix, and endometrium. All the patients experienced activity in the breasts, especially when uterine bleeding appeared, or at the times when they had the feeling that menstruation would occur. These changes were constant and increasingly prominent throughout the duration of treatment. At the end of twenty-eight days, when the second curetting was done, there was present in all cases congestion of the cervix characterized by a purplish-red enlargement and increased vascularity. At the third curetting, which was performed at the end of fifty-six days' treatment, there was noted a definite increase in the thickness of the endometrium. This thickness was roughly proportional to the amount of theelin administered, while those patients who had had the massive doses were found to have an atypical endometrium with complex glands with intrapapillary processes, and a great increase in the stroma where there was congestion of the vessels. The fourth curetting showed similar but exaggerated results in all patients.

Werner and Collier deduced from these results that the degree of endometrial growth was directly proportional to the duration of administration and to the size of dose. Thus one patient showed endometrial growth at the end of twenty-eight days as a result of having had 2,800 rat units of theelin. Another patient first showed growth at the end of fifty-six days, at which time she also had had 2,800 rat units administered, so that that figure would appear to be the minimum clinical dose. Kaufmann and the Guy's observers had used one and a quarter million international units, or 50,000 rat units, for their experiments, but the end-points were very dissimilar—Werner and Collier had the progress controlled by endometrial scrapings, Kaufmann by true menstrual bleeding. Werner and Collier, however, had not tried to produce menstruation as they had not followed up the theelin by corpus luteum extract; but since they definitely stated that they obtained endometrial growth after only 2,800 rat units, or 75,000 international units of theelin, it seemed to me that a dose of oestrin between 75,000 and one and a quarter million international units, followed by corpus luteum extract, ought to be sufficient to produce menstruation in an ordinary case of secondary amenorrhoea, if not in a castrated woman, and so I decided to try three-quarters of a million international units as a start on four cases. One of these four cases was castrated, and therefore the dose decided upon would probably be ineffective, but would act as a control; if, however, it was not ineffective but a success, then three-quarters of a million units would be a sufficiently big dose, and the previous doses used would be proved to be too large.

Technique

The dose was spread out over a fortnight and followed by corpus luteum extract as advocated by Bishop, Cook, and Hampson, their technique being followed exactly except for the smaller dosage. The extracts used were oestroform B and progestin, both products of British Drug Houses Ltd. A course of treatment consisted of injecting 150,000 international units of the oestroform B on the first, fourth, eighth, eleventh, and fifteenth days, and then one rabbit unit of progestin on the nineteenth, twentieth, twenty-first, twenty-second, and twenty-third days—the whole course taking twenty-three days to complete. As will be seen when the cases are described, not one of the four patients menstruated, although every one had some response, either by aching pains and a feeling of premenstrual discomfort or by general mental elevation.

Having had four failures with this smaller dose, for the second course of treatment all the patients had the full complement of oestrin as recommended by Kaufmann and others, and this was given after one month's rest. As a result of the two courses two of the patients menstruated and the other two were greatly improved although they never menstruated, one of them being the castrated woman. This patient had very similar pains to those she had had previously when she suffered from dysmenorrhoea, and these were a sufficiently powerful deterrent to make her give up any further treatment. The description of the various cases is as follows:

CASE I

A married woman, aged 27, complained of amenorrhoea for the last nine months. Puberty was at the age of 18, and her periods had always been irregular with occasional amenorrhoea, the longest previous lapse being for six months. Her periods usually lasted five to seven days and were sometimes accompanied by pain on the first day. She had been married for three years, but there had been no conception. She had a petite, boyish figure with small flat breasts; the secondary sexual characteristics were quite well developed. The uterus was small and acutely anteverted; the cervix long and narrow with a small external os. The general impression given was one of genital hypoplasia with an adolescent or pubescent uterus.

Treatment was started in April, 1935, with the injection of 150,000 international units of oestroform. At the end of the course there was no appreciable result. A second course was begun in early May with the dose increased to 250,000 units. When this was completed there was still no menstruation, but the breasts were larger, the figure much more mature, and the libido was increased. Cases of hypoplasia, such as this one, need large amounts of oestrin, and as there had been some improvement, a third course was given, the dose being the same as in the second. Five days after this was ended a period started. This was normal in every respect and lasted for six whole days. There has, however, been no further success.

CASE II

An unmarried woman of 24 complained of five months' amenorrhoea. There was no history of any previous amenorrhoea, and she had a normal gynaecological history. Examination showed her to be well developed and healthy; there was marked facial hirsuties but no other abnormality was detected. The uterus was about normal in size; the cervix was normal and the fornices were clear.

Treatment was started, as before, with 150,000 units, and again there was no appreciable result. After the standard course had been given one month later, a period began the day before the last injection was due, on June 14th, and lasted five full days, which was the normal previous duration. The next month there were the usual aches and discomforts which had previously heralded the on-coming of the menstrual period, but there was no flow. One week after this lapse the treatment was again begun, and on the last day of the injections another perfectly normal period started (August 17th). Since then there has been one further period in October without any treatment at all.

CASE III

An unmarried woman, aged 37, five years previously had had intrauterine radium applied for 1,805 mg.-hours in order to produce what was hoped would be a temporary menopause. This was done for very severe and intractable dysmenorrhoea. Since that operation she had put on weight steadily, the periods had ceased entirely, and for one month immediately after the radium application she had hot flushes. She wished to have her periods restored to her if possible, as she had recently become engaged to be married. Her breasts were large, though there was not much actual glandular tissue palpable. There was a decrease of the vaginal mucous secretion; the cervix was normal, the uterus small and anteverted, its internal length being one and a half inches instead of the usual two inches.

Treatment was started in March, 1935, with 150,000 international units of oestroform B. When this was finished the only result was that the patient stated that she felt brighter

and more alert mentally, and more physically active than she had done ever since the insertion of the radium. Three weeks after this course was completed a second one was started with 250,000 units, and after she had had the fourth injection the patient complained that she had had colicky pains which lasted for six hours. After the fifth injection (the last one of oestroform) the pains began again and were very severe and similar to those she had had with her periods previously. These lasted intermittently for five or six days, during which time the progestin was given without either starting her period or alleviating her pain. Except for the improved mental outlook, which had persisted, and the dysmenorrhoeic pains, there was no result, and the patient, having had a reminder of her dysmenorrhoea, would not continue with the treatment.

CASE IV

An unmarried woman, aged 22, complained of amenorrhoea which had lasted since December, 1932. Puberty was at the age of 14, and she had had normal periods for four days in every twenty-eight days for two years. There was then a pause for nine months, during which time she was treated by her panel doctor. The periods then returned exactly as before and were consistent and regular until December, 1932, since when there had been absolute amenorrhoea. During 1933 she had twelve months' treatment, which included drugs such as calcium and iron, and such hormones as thyroid extracts and antuitrin S (a Parké Davis extract of the pituitary hormone which stimulates the corpus luteum). None of these had had the slightest effect. The patient herself looked very small, thin, and undernourished, and had a rather quiet and nervous disposition, but apparently she was being paid well as a book-keeper and was above average intelligence. The hymen was intact, the cervix and uterus small but within normal limits, and the appendages were normal.

Treatment was started in March and, as in the other three cases, 150,000 units were given in the first course and 250,000 units in the second. The primary course was without results and the second was started after a month's rest. This was also without effect, except for the fact that the patient stated she felt better than she had done for two years. The impression given by the patient was that the cause of her amenorrhoea was mental rather than a primary breakdown of her endocrine system, but she would admit of no emotional trouble or problems of any kind, and the case must be written down as a failure. It is possible that the amenorrhoea was only a symptom associated with anorexia nervosa.

Conclusion

Summing up the four cases just described, two of them can be counted as successes in that a normal period was produced in each patient following treatment; one of them had three normal periods, two immediately following a course of injections, and the other six weeks after the last period without any treatment at all. The third case, that of the castrated woman, is difficult to assess justly. One cannot say that there were changes in the genitalia, but there were definite premenstrual pains, and even the dysmenorrhoea itself without the menstrual flow. It is idle to speculate what another course of treatment would have resulted in, but without it the case must be called incomplete rather than a failure, because there were definite indications that another course was justified. The remaining case, as has already been mentioned, was a failure. That leaves two successes, one incomplete success, and a failure.

Considering that a course of treatment, following the technique described, costs about four guineas, and that to guarantee a result at least two courses are necessary, most probably three, it is obvious that this treatment can only be administered to a chosen few. Even then it is probable that only two or three periods will result in the majority of cases. However, it is not so much the therapeutic value of the work of Kaufmann and the others that counts, but rather the experimental knowledge of the endocrine functions of the ovary and corpus luteum.

As a result of their experiments some very definite conclusions and facts can now be said to be in our possession, facts which, even though they were surmised and embodied in hypotheses beforehand, had not been conclusively proved. That the primary hormone of the ovary, oestrin, is responsible for the growth and development of the uterus is now beyond dispute, and by the administration of massive doses of this hormone many a young woman, who ordinarily would have been condemned to a sexually immature, sterile, and probably dysmenorrhoeic life, can now be cured and made normal; just as a potential cretin can be saved by early medication with thyroid extract. The oestrin produced by the ovary is therefore responsible for the growth of the uterus and endometrium, and if this is in excess of the normal, then cystic hyperplasia of the endometrium develops. This is seen in the condition of metropathia haemorrhagica, where one ovary is fibrosed and functionless and the other is cystic and producing oestrin but not forming corpora lutea and hence no progesterin. Progesterin during the last ten to fourteen days of the intermenstrual period is essential for the production of a normal endometrium capable of receiving and embedding a fertilized ovum, and is therefore an integral part of the therapeutic technique.

The balance between oestrin and progesterin is interesting; Kaufmann thought that thirty-five rabbit units of progesterin were necessary, but the English writers state that only five units are needed to produce true menstruation, and the latter appears to be the correct figure. The dosage of oestrin varies with the different workers. Bishop, Cook, and Hampson at Guy's and Kaufmann at Vienna use one and a quarter million international units and the Americans, Werner and Collier, much less. The latter state with certainty that 75,000 international units are the minimum clinical dose of oestrin, but for true menstruation they maintain that nearly a million units are essential. There is almost certain to be a considerable margin of error or discrepancy between the figures of the various workers as each one uses a different preparation, and, even if they are all standardized, it seems doubtful if the products retain their potency with keeping, and the standard itself is open to individual variations of value.

REFERENCES

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- ² Idem.: *Lancet*, 1934, i, 399.
- ³ Bishop, R. M., Cook, F., and Hampson, A. C.: *Ibid.*, 1935, i, 139.
- ⁴ Werner, A. D., and Collier, W. D.: *Journ. Amer. Med. Assoc.*, 1933, c, 633.

J. Karaseff (*Journ. de Radiol. et d'Électrol.*, July, 1936, p. 373) found radiographic changes in the bones and joints in 95 per cent. of all cases of leprosy. The changes affect mainly the distal ends of the extremities. They are of a destructive nature. They appear under two different forms: (1) local osteoporosis, seen mainly in persons of the hyposthenic type; (2) osteo-articular destruction, seen only in pronounced cases of leprosy of the nervous system. These changes are met most frequently in the feet. The spine is never affected in leprosy. The bone changes become more pronounced with the general progress of the disease.

L. M. Ruiz (*Arch. Med., Cir. y Esp.*, May 30th, 1936, p. 354), who records an illustrative case, maintains that mononucleosis is of importance in the diagnosis of malaria, and should be studied whenever the presence of the plasmodium cannot be demonstrated. In quotidian fever and atypical forms of malaria a diagnosis must be made from other diseases, especially acute leukaemia and glandular fever or infective mononucleosis. Apart from its diagnostic value a differential leucocyte count is indispensable in the examination of a case of malaria, as the neutrophil picture is a guide to the patient's resistance.

THE PROBLEM OF OTOSCLEROSIS

BY

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The clinical picture of otosclerosis is so indefinite, its symptoms are so often shared by other forms of deafness, and its physical signs are so few and inconstant, that the diagnosis can only be made with varying degrees of probability. When it is added that no treatment is known that has the slightest effect on its course it might well be supposed that the worst had been said. Nevertheless, by constantly diagnosing the disease on insufficient data and by persisting in its treatment otologists have added an aspect to the subject which carries with it something more than the reproach of an unsolved problem.

The outstanding pathological features of otosclerosis are: the bony fixation of the stapes, the occasional involvement of the basal coil of the cochlea, and, though this has not yet been proved, degenerative changes in the auditory nerve. According to the relative time incidence of these factors the clinical picture of otosclerosis may, apparently, vary from that of a middle-ear "obstructive" deafness to that of pure nerve deafness. Moreover, this picture need not possess one symptom that is not constantly present in other and far more common types of deafness. The facile diagnosis of this disease is almost as great a mystery as its aetiology.

The Bezold Triad

For the past fifty years otologists have reiterated the statement that a case of progressive deafness with the Bezold triad and nothing obvious to account for it is otosclerosis. This "triad" consists of: increased bone conduction, negative Rinne, and loss of low note perception. As the increased bone conduction is caused by the loss of low note perception, and as the "negative Rinne" is merely a quaint way of expressing this ratio, it is not very obvious why there should be this insistence on its being three signs instead of only one. At the best this "syndrome" can only be of diagnostic value in uncomplicated cases in which fixation of the stapes precedes any serious involvement of nerve or cochlea. Yet it is made to apply to cases in which otosclerosis is supposed to coexist, as well it may, with conditions known themselves to produce the Bezold "triad"—that is to say, middle-ear deafness or loss of low note perception.

There are certain other features of otosclerosis the diagnostic value of which I will briefly attempt to assess. It will be noticed that they may all be absent in otosclerosis, while, with very few exceptions, even their presence only becomes significant in the aggregate.

Other Diagnostic Features

The Family History.—At least half the cases are diagnosed in the absence of any family history. Unless it can be investigated, and this is rarely possible, even its presence must often be misleading.

Age of Onset.—Although the disease usually starts round about puberty, it may start at any other period. It has been found, and verified microscopically, in the seven-months foetus, to say nothing of intervening and later stages. Nager cites a case in which recent deafness in a man of 70 was diagnosed as otosclerosis. In the individual case, therefore, the time of onset can scarcely be of more assistance in diagnosis than the greater incidence in the female sex.

Course of the Disease.—Although the deafness in otosclerosis is progressive, it is not uniformly so. There may