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In maintaining the flow of arms and munitions the health and well-being of the industrial worker is clearly of the utmost importance, and no single factor has greater influence than the provision for nourishing and attractive meals during the hours of work. Industrial canteens have long been established, but the conditions of war production are likely to increase their usefulness greatly and to add to the number of firms who find it necessary to make arrangements for meals during working hours. The extension of the hours of work, the increase of night shifts, difficulties in transport, "black-out" conditions, all contribute to the strain of war-time production; the evacuation of the family often includes the wife of the industrial worker, and the industrial canteen to-day not only meets the needs of the workers during work hours, but in many factories canteens are already providing facilities for breakfasts and suppers for those workers who are left without anyone in their homes to prepare these meals. How best to organize canteen facilities is the practical question which the Industrial Welfare Society has attempted to answer in a booklet, *Canteens in Industry*, issued at 1s. from 14, Hobart Place, S.W.1. Though primarily concerned with the organization of canteens in industrial concerns, most of the booklet should be no less useful to those responsible for the provision of meals in schools, hospitals, or other institutions, or to those now arranging meals for evacuated school children and mothers and for A.R.P. workers.

PRODUCTION OF ANTIGONADOTROPHIC ACTIVITY IN MAN BY INJECTION OF EXTRACT OF PREGNANT MARES' SERUM

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The presence of a gonadotrophic substance in the serum of mares during the second and third months of pregnancy was discovered by Cole and Hart (1930). Highly purified extracts are now prepared from this source and are used clinically for various manifestations of hypogonadotrophism. In common with gonadotrophic extracts of the anterior pituitary gland and of human urine of pregnancy, the prolonged injection of extract of pregnant mares' serum to animals of a different species from that from which the preparation originated does not cause prolonged stimulation of the reproductive organs (Meyer and Gustus, 1935). This refractoriness is caused by the appearance in the blood of inhibitory substances, which can be demonstrated by the fact that the serum of desensitized animals has the power to inhibit, in other test animals, the activity of the extract in question.

The formation of these substances in the blood as the result of prolonged treatment with gonadotrophic extracts is likely to set a limit to their use as therapeutic agents. It was observed previously, however, by Spence, Scowen, and Rowlands (1938) that the prolonged administration to human patients of extracts prepared from the urine of pregnant women did not evoke the formation of these inhibitory substances, so that treatment could be carried on indefinitely. The presence of such inhibitory substances in the blood of man treated with extract of the serum of pregnant mares does not seem to have been demonstrated, but, as will be seen below, they are undoubtedly produced. It is obvious, therefore, that to continue treatment after such substances have formed would be futile, as most, if not all, of the extract would be neutralized in the circulation. Until a level of dosage and a method of spacing the injections have been found which will not induce the formation of these inhibitory substances care must be exercised in the clinical use of extracts of pregnant mares' serum.

Methods

PRODUCTION OF ANTISERUM

Nine patients with undescended testes were injected intramuscularly with a gonadotrophic extract prepared from the serum of pregnant mares by N.V. Organon (Oss, Holland). The extract was assayed in "rat units" by the manufacturers, there being at that time no international unit. An international standard and a unit defined in terms thereof are now being established,* however, and enough information is available to allow of an approximate estimate of the activity, in international units, of the serum preparation used. The manufacturers stated that 150 µg. was equivalent to 1 "rat unit," but the dosage

* See Bulletin of the Health Organization of the League of Nations, 1938, 7, 894.

is recorded here in milligrammes—1 mg. being found to be approximately equal to 80 international units.

Three of the patients (Nos. 32, 19, and 18) were injected daily for twelve weeks with 6, 12, and 13.5 mg. respectively. The remaining six patients were divided into two groups: (a) three (Nos. 24, 25, and 26) who were injected with 18 mg. twice weekly for twelve weeks; and (b) three (Nos. 22, 23, and 27) who were injected with 36 mg. twice weekly for a similar period.

Immediately before treatment blood samples were taken from the median basilic vein, and subsequently as near as possible four, eight, ten, and twelve weeks after treatment was begun. To determine the rate of disappearance of the substance, samples were also taken, usually two, four, and eight weeks, and if necessary at a later stage, after treatment.

BIOLOGICAL ASSAY

The extract of pregnant mares' serum used in all the biological assays was the same as that employed in the production of the antisera. The extract was assayed for gonadotrophic activity by its ability to increase the weight of the ovaries of the immature rat. Groups of ten to twenty rats weighing 40 to 50 grammes were injected subcutaneously once daily for five days with different amounts of extract. The animals were killed twenty-four hours after the last injection, and their ovaries and uterus dissected, fixed in Bouin's fluid overnight, and on the following day weighed from 70 per cent. alcohol. A dose/response curve was drawn from the results, which are given in Table I. The antigonadotrophic activity of the serum was assayed by its ability to inhibit this response to the gonadotrophic extract when injected simultaneously.

TABLE I.—*Gonadotrophic Activity of the Extract of Pregnant Mares' Serum*

Number of Rats per Group	Total Amount of Extract Injected (mg.)	Average Weight of Ovaries (mg.)
10	0	10
20	0.25	33
10	0.375	56
20	0.5	91
10	0.75	131
10	1.0	203

In all tests on the inhibitory activity of the sera a standard total amount of 0.5 mg. of extract was injected. Both serum and extract were injected into groups of five immature female rats once daily for five days; injections were made into opposite flanks of each animal. The ovaries were weighed as described above. The antigonadotrophic activity of the serum was determined as follows:

An amount of serum was injected which was estimated to cause a partial reduction in the response (weight) of the ovaries to the standard amount of extract. From the dose/response curve the amount of extract was calculated which, given alone, was required to produce the same ovarian weight as that resulting from the combined injection. The difference between this calculated amount and 0.5 mg. would therefore represent the amount of extract inhibited by the quantity of serum injected into the test rat. The results are expressed throughout as the number of milligrammes inhibited by 1 c.cm. of serum.

Results

The Development of Antigonadotrophic Activity.—The results obtained are shown graphically in Figs. 1-3. No

FIG. 1.—Antigonadotrophic activity of the serum of three patients injected daily with extract of pregnant mares' serum. × = patient No. 32, injected with 6 mg.; ● = patient No. 19, injected with 12 mg.; ○ = patient No. 18, injected with 13.5 mg.

The arrow in each figure indicates the time when treatment was stopped.

FIG. 2.—Antigonadotrophic activity of serum of three patients injected bi-weekly with 18 mg. of extract. × = No. 24; ● = No. 25; ○ = No. 26.

FIG. 3.—Antigonadotrophic activity of serum of three patients injected bi-weekly with 36 mg. of extract. × = No. 22; ● = No. 23; ○ = No. 27.

antigonadotrophic activity could be detected in the serum of any of the patients before treatment began. After about six weeks' treatment, whether by daily or by twice-weekly injection, the serum of most of the patients contained some antigonadotrophic activity, which, on the whole, rapidly increased throughout the remainder of treatment. In most patients little, if any, increase in the activity occurred after the treatment was stopped. However, the activity of the serum of two patients (Nos. 22 and 27) injected with 36 mg. twice weekly continued to rise for another four weeks. One week after the end of treatment 1 c.cm. of each serum neutralized 1.8 and 1.35 mg. of extract respectively, whereas three weeks later the same amount of serum inhibited 3.3 and 2.85 mg. respectively. The total volume of serum being assumed to be 1.5 litres, it can be calculated that about 4.5 grammes of the extract would be neutralized completely by the total antigonadotrophic activity in the blood of each of these patients. Each patient had received only 0.864 gramme of extract. The antigonadotrophic substance in the circulation alone at the end of the course was therefore enough to neutralize more than five times the total quantity injected. After reaching its maximum the activity diminished, at first rapidly, but subsequently more gradually, so that in most cases it was still demonstrable three months or more after treatment was terminated.

Specificity of the Action of the Serum.—Some antigonadotrophic sera, in addition to inhibiting the action of the extracts used in their production, can also inhibit the action of gonadotrophic extracts prepared from other sources. A number of cross-reactions between various extracts and their antisera carried out by Rowlands (1938) showed that an antiserum prepared in rabbits to an extract of pregnant mares' serum was highly specific in that it inhibited only extracts prepared from this source. This specificity was also observed in the present experiments. Thus the serum of patient No. 18, at the time when it contained its maximum antigonadotrophic activity, did not neutralize the action of extracts of human pituitary tissue or human urine of pregnancy. The results are summarized in Table II, which shows that the simultaneous administration of the antiserum did not reduce the response of the ovaries of rats injected with the extracts of human origin. It is concluded, therefore, that the antigonadotrophic substance present in the blood of patients treated with extracts of pregnant mares' serum would not inhibit the gonadotrophic hormone secreted by the patients' own pituitary glands, nor is it likely to inhibit the action of gonadotrophic extracts prepared from other sources. Some proof of this was obtained clinically.

TABLE II.—*The Effect of Antiserum to Extract of Pregnant Mares' Serum on the Gonadotrophic Activity of the Human Pituitary Gland and on that of the Urine of Pregnant Women*

Extract Given	Total Amount of Extract Injected (mg.)	Serum Given	Total Amount of Serum Injected (c.cm.)	Average Weight of Ovaries (mg.)
Human pituitary gland (AP 47)	2	—	—	40
" " "	2	No. 18	1	42
Urine of pregnancy (UP 10)	1	—	—	30
" " "	1	No. 18	1	30

Clinical Effect of Extract of Pregnant Mares' Serum.—In none of the patients was any improvement in the position of their testes observed at the end of twelve weeks'

treatment. This might be due to an inherent ineffectiveness of this type of gonadotrophic extract for this condition, but it seems much more probable that it is the result of the development of refractoriness. If this were so, then the extract which was injected would almost certainly be neutralized in the blood of the patient, thus rendering it ineffective. Three months after treatment with extract of pregnant mares' serum was discontinued, treatment with bi-weekly injections of gonadotrophic extract of human urine of pregnancy ("pregnyl") was instituted. As the majority of the patients have only just begun this form of therapy a full description must be deferred. It may be mentioned, however, that of three patients (Nos. 18, 19, and 23) who have received the full course of treatment with the urinary extract, two (Nos. 18 and 19) responded favourably, a successful result being obtained after two and four months respectively. Three other patients with undescended testes, whose blood was not assayed for antigonadotrophic activity, were treated with extract of pregnant mares' serum for twelve weeks, two patients receiving 18 mg. and one 12 mg. intramuscularly twice weekly. At the end of treatment no improvement was observed. They were then treated with extract of human urine of pregnancy without any intervening rest period between the two forms of therapy. A successful result was obtained in one patient after two and a half months.

Thus three patients who did not respond to extract of pregnant mares' serum responded subsequently to extract of human urine of pregnancy, in spite of the presence in their blood of a substance inhibitory to the former extract. This, therefore, is a further demonstration of the specificity of the antigonadotrophic substance produced by extract of pregnant mares' serum, and, although the number of cases so far is small, it suggests that extract of human urine of pregnancy is more effective than extract of pregnant mares' serum in treating this condition.

Discussion

The data recorded above provide information on two points—(a) the relation between amount and method of dosage and degree of antigonadotrophic activity evoked, and (b) the rate of disappearance of this inhibitory activity after the end of treatment. It appears that the degree of antigonadotrophic activity is not proportional to the amount of extract injected. The activity of the serum of the patients treated with bi-weekly injections was nearly twice as great as that of the patients given daily injections, although the latter received the same or even greater total amounts. Moreover, the activity of the serum of patient No. 32, who was injected daily with 6 mg. of extract, was as great as that of either of the other patients injected daily with 12 and 13.5 mg. respectively. The method of bi-weekly injections appears to be more conducive to the formation of inhibitory sera, as shown by the fact that the activity of the serum of two of the patients injected with 18 mg. of extract twice weekly was greater than that of the serum of the patients injected with 13.5 mg. daily—two and a half times the total weekly amount.

The intensification of antigonadotrophic activity after the treatment had been discontinued, such as was observed in two of the three patients who received the larger bi-weekly injection, is unusual in our experience. It is difficult to explain why it should have occurred in these patients and not in Nos. 18 and 19, who were injected with an even greater weekly amount of extract. Until further confirmation of this is forthcoming it would be premature to discuss the significance of this finding.

Summary

Antigonadotrophic activity was demonstrable in the serum of nine patients with undescended testes who were injected intramuscularly, either daily or twice weekly, for twelve weeks with an extract of the serum of pregnant mares.

The antigonadotrophic activity (a) developed after four to six weeks' treatment, and subsequently in most cases rose rapidly; (b) was not proportional to the amount of extract which was injected; (c) usually decreased at the end of treatment, but was still present for three months or more—in two patients, however, activity increased for about three weeks after injections were discontinued; (d) was greater in patients who received twice-weekly injections of extract.

The previous observation of Rowlands (1938) on the specificity of a similar antiserum, raised in rabbits, was confirmed. The human antiserum did not inhibit, in immature rats, the action of extracts of either human pituitary gland or urine of pregnancy.

No improvement in the position of the testes of the patients was observed during treatment with this extract, but in three of six patients subsequently treated with extract of urine of pregnancy descent of the testes was successfully obtained.

We desire to thank Dr. A. N. Macbeth of N.V. Organon for supplies of the extract of pregnant mares' serum and extract of human urine of pregnancy ("pregnyl").

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BRONCHOGRAPHY*

BY

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Bronchoscopy has its limitations. For example, the upper lobe bronchus, except for a very small portion at its mouth, cannot be explored, and the lesser bronchi of the middle and lower lobes are too narrow to permit the passage of a bronchoscope. As pulmonary disease frequently affects just those parts which are invisible, how can this difficulty be overcome? Bronchography will, to some extent, provide a remedy. By the injection of radio-opaque oil the whole bronchial tree can be demonstrated with little or no distortion on the fluoroscopic screen. The projection of a mere shadow cannot, of course, have the accuracy of direct vision, but it is an excellent substitute. Originally it was for therapeutic reasons that lipiodol was injected into the lung by Lafay (1901). Twenty-one years later it was advocated as a contrast medium by Sicard and Forestier (1922).

Clinical Application

The importance of bronchography has developed with the advance of thoracic surgery. In bronchiectasis the smaller bronchioles beyond bronchoscopic vision are prin-

cipally affected, and great scope is therefore provided for bronchography. It is upon the injection of radio-opaque oil that we must rely for confirmation of the diagnosis and for the determination of the extent of the lesion.

Neoplasms also afford a considerable field for bronchography, especially as there may be no endoscopic signs when the smaller bronchi are invaded. Now these are the cases most suitable for operation. A bronchogram demonstrating blockage of a bronchiole, taken in conjunction with clinical and other radiological signs, will make diagnosis of neoplasm possible at a stage when lobectomy holds out a good prospect of success. Investigation of an obscure shadow seen in the radiological examination of the chest may call for the determination of its relation to the bronchial tree on the one hand and the mediastinum on the other. Here a bronchogram is most helpful, particularly if bronchoscopy has been negative.

Interpretation

Nowadays lobectomy is being more frequently performed for the treatment of bronchiectasis, and the accurate interpretation of a well-taken bronchogram is essential for the success of the thoracic surgeon. In bronchiectasis the ideal case for lobectomy would be one confined to a lower lobe, and it is as well to point out here that lobectomy will fail in such a case if cavitation of the lingula has escaped recognition. Bronchography alone will avert this and enable the surgeon to deal with the lower lobe and the lingula at the same time. To investigate a case completely a series of bronchograms of both lungs is essential.

It must be realized that in the antero-posterior film the upper lobe overlaps the greater part of the lower lobe, and it may be impossible to determine whether a dilated bronchus lies in the upper, middle, or lower lobe. A lateral film is therefore a *sine qua non*, and only one lung must be delineated, otherwise the bronchial shadows of the opposite side will obscure the view. Stereoscopic pictures are difficult to obtain and have not proved of the same value in bronchography as in ordinary chest photography.

Technique

To satisfy the requirements of the surgeon the injection of radio-opaque oil must be confined to one lung, or even one lobe of a lung. There is a choice of two methods: the oil may be injected under direct vision through a bronchoscope or through a catheter inserted into the bronchial stem under fluoroscopic guidance. The bronchoscopic method has been extensively used but has drawbacks, as pointed out by C. L. Jackson and Bonnier (1937) of Philadelphia. I will quote their words: "Too much of the lipiodol was coughed out, especially in children; and often there was some delay in transportation of the patient to the x-ray department or in taking the picture." The instillation of lipiodol by means of a catheter passed into the trachea was first described by Iglaue (1926), and modifications of the method have been in use ever since. By this means radio-opaque oil can be delivered into any part of the bronchial tree under fluoroscopic control. The manipulation is simple and is free from danger. Attention to detail is, however, essential to success.

In adults the pharynx and larynx are anaesthetized with 10 per cent. cocaine or one of its substitutes. My preference is for 2 per cent. decicaine (pantocaine), which produces sufficient anaesthesia and is less toxic. A fine spray is used for the pharynx, and for the glottis either a laryngeal spray or the fractional instillation of Luken, which has the advantage of anaesthetizing the trachea and thus inhibiting the cough reflex. A soft rubber catheter

* Read in opening a discussion in the Section of Oto-rhino-laryngology at the Annual Meeting of the British Medical Association, Aberdeen, 1939.