Trichinosis in South-west Ireland

JOHN P. CORRIDAN,* M.D., D.P.H., D.I.H.; JOHN J. GRAY,† M.B., B.SC., D.P.H.

British Medical Journal, 1969, **2**, 727–730

Summary: Since the large outbreak of trichinosis in Liverpool in 1953 there have been three outbreaks in Ireland, two occurring recently in Cork and Kerry, where a total of 76 cases was confirmed. In the outbreak of 50 cases in Kerry the latex trichina slide agglutination test was found to be valuable diagnostically and epidemiologically, while the efficacy of thiabendazole treatment was not established. This infection may be maintained as a reservoir in wild carnivores, occasionally spreading to pigs and perpetuated in them by a failure to boil pig swill.

Introduction

With the exception of three cases in Lewisham in 1955 (McGill, 1957) no records of trichinosis have been published in Britain since the Liverpool epidemic (Semple *et al.*, 1954). Since then, however, there have been three outbreaks in Ireland—eight cases in Tipperary (Nash *et al.*, 1957; Drury, 1957), 26 in Cork (Corridan and O'Meara, 1968), and 50 in Kerry. Some features of both the Cork and Kerry outbreaks are discussed, but this report is primarily concerned with the latter outbreak, which provided an opportunity to study (*a*) the differential diagnosis of trichinosis with particular emphasis on the symptomatology as seen by general practitioners; (*b*) the diagnostic value of the latex trichina slide agglutination test; (*c*) the value of thiabendazole for treatment; and (*d*) the epidemiology of the disease with cases occurring over a wide area, for, despite the repeated outbreaks in Ireland, nothing is known about the maintenance cycle of the infection in interepidemic periods.

Methods of Diagnosis

Trichinosis is a disease of remarkably varied symptomatology, course, and severity; consequently a sporadic case may be difficult to diagnose unless one bears the disease in mind or has previously seen a case. Hall (1937) listed 50 diseases which were mistakenly diagnosed in patients ill with trichinosis. A clinical diagnosis of trichinosis without confirmatory evidence is insufficient, but may be acceptable in an epidemic, especially if periorbital oedema is accompanied by generalized myalgia, pyrexia, and eosinophilia. Initially confirmation must be sought by muscle biopsy, and subsequently cases can be diagnosed by serology.

Serological Tests

These include precipitin, complement-fixation, flocculation, and agglutination tests and the fluorescent trichina antibody test. Precipitin, complement-fixation, or flocculation tests become positive after the third week (Aikawa, 1966). Consequently a negative followed by a positive test or a rising titre is of great diagnostic significance. The latex trichina slide agglutination test supplied by Hyland Laboratories became commercially available in Ireland in 1967 and was used because of its simplicity. In their description of this test Innella and Redner (1959) stated that the degree of specificity obtained remarkably paralleled that obtained with the complement-fixation test and in most cases was more sensitive.

In the Cork outbreak the latex test was performed in 23 patients. It was positive in 19, became positive following an initial negative reaction in three, and was negative when performed five months after the illness in a patient with a positive result from a muscle biopsy. All 50 patients in the Kerry outbreak had positive latex tests. Towards the end of May 1968, when the area was undergoing its final fine-combing, people who had presented as classical clinical cases in January and February were seen, but as their latex tests were by then not unexpectedly negative they were not accepted for the purpose of this report. In one family the index clinical case had a negative and five others a positive test. The number of confirmed cases in the Cork and Kerry outbreaks would not have reached 76 had this test, which in the investigation of trichinosis is a valuable epidemiological tool, not been used. Norman and Kagan (1963) suggested that, because it is easy to perform yet offers a high degree of accuracy, it may be the test of choice for the laboratory receiving only the occasional specimen of serum.

Adequate case-searching is essential in any outbreak. A personal visit to individual doctors takes precedence over any diagnostic test in tracing cases. When a suspected case is seen it is essential to ask if other members of the household had a similar if less severe illness. This question brought many cases to light.

Clinical Manifestations

Trichinosis usually has three stages:

Intestinal Stage: During this period, which lasts about a week, there may be nausea, vomiting, diarrhoea or constipation, abdominal pains, and a feeling of malaise.

Muscular Invasion: This is the stage of generalized pains, pyrexia, periorbital oedema, and toxaemia, and may last from less than a week to six weeks. Signs of myocarditis or encephalitis may also occur.

Convalescence: The fever abates and pains lessen as encysted larvae become encapsulated. Recovery, which may take some months, is usually complete.

The 50 cases confirmed in Kerry were seen by one of us and the clinical picture was supported by hospital findings where available. About one-third were not seen by any doctor until they had recovered. Their symptomatology was elicited by means of a detailed questionary and from questions to relatives.

Symptomatology

According to Gould (1945) the symptomatology of trichinosis varies with the number of viable larvae ingested, the size and age of the patient, the tissues invaded, the general state of health of the individual, the presence of other morbid states, and the length of the incubation period.

Table I shows the frequency of symptoms and signs in the 50 patients.

Periorbital oedema is one of the commonest, and classical, findings in trichinosis. In one patient the oedema, which had disappeared, recurred.

* Lecturer in Social and Preventive Medicine, University College, Cork.
† County Medical Officer, Tralee, Co. Kerry.

Gastrointestinal Symptomatology.—Fewer than half had either diarrhoea or constipation. Diarrhoea, however, was nearly twice as common as constipation.

TABLE I.—*Frequency of Symptoms and Signs in 50 Cases*

	Cases			Cases	
	No.	%		No.	%
Periorbital oedema	46	92	Pains in joints	9	18
Lethargy	37	74	Dyspnoea	9	18
Headache	35	70	Rash	8	16
Pains "all over"	34	68	Constipation	7	14
Swelling of face	34	68	Loss of memory	6	12
Pyrexia	33	66	Conjunctivalhaemorrhage	5	10
Anorexia	33	66	Albuminuria	4	8
Sweating	33	66	Sense of impending death	4	8
Pains in legs	32	64	Improved appetite	3	6
Pains in arms	32	64	Trismus	2	4
Thirst	32	64	Alopecia	2	4
Chilliness	22	44	Venous thrombosis	?2	4
Dizziness	21	42	Swelling of hands	1	2
Photophobia	20	40	Hemiplegia	1	2
Chemosis	19	38	Monoparesis	1	2
Sore throat and/or tongue	18	36	Palatal paralysis	1	2
Nausea	18	36	Facial paralysis	1	2
Insomnia	17	34	Delirium	1	2
Cough	16	32	Atelectasis	1	2
Vomiting	15	30	Diplopia	1	2
Diarrhoea	13	26	Oliguria	1	2
Lymphadenopathy	11	22	Abdominal distension	1	2
Swelling of legs	10	20	Enlarged heart	1	2

Myalgia.—Pains in the legs and arms were equally common and those with generalized pains usually related them to the back and neck. Most of those with muscular pains also complained of stiffness, some being unable to walk unaided.

Pyrexia.—Not all were seen by a doctor during the acute stages of the illness and therefore pyrexia was confirmed in only 33. The maximum temperature in those patients in hospital was 104·2° F. (40·1°C.). One patient treated at home had a temperature of 105° F. (40·6° C.).

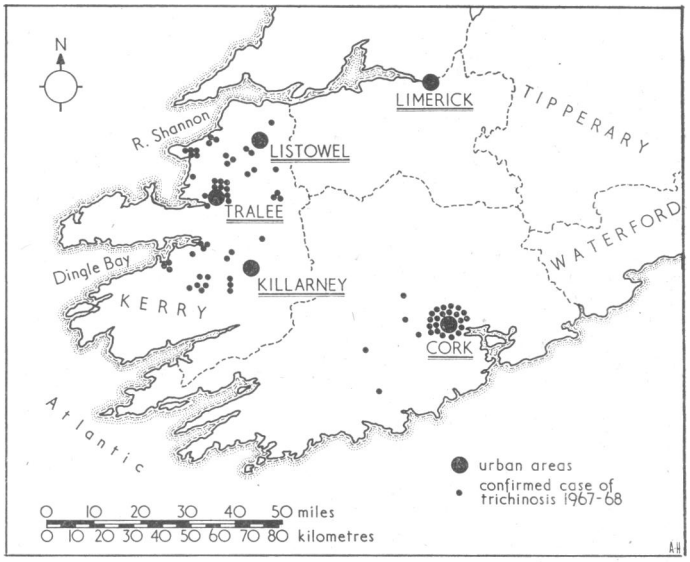
Other Symptoms and Signs.—Cough occurred in 16; eight had a rash, either erythematous or macular and often confined to part of the body or a limb; 11 had cervical lymphadenopathy; four thought they were dying and would possibly not survive the night; and four had transient albuminuria. Alopecia developed in two women during convalescence, but the hair regrew in both. Vascular thrombosis, which is a recognized complication of trichinosis, occurred in two women; one had a deep femoral thrombosis, while the other, who was pregnant, had phlebothrombosis, though the thrombosis was more likely to have been associated with her pregnancy. One seriously ill patient, though having no E.C.G. changes, showed clinical evidence of myocarditis. Similarly another patient with a pulse rate of 120 and some irregularity and with equivocal E.C.G. changes may also have had myocarditis.

Eosinophilia.—Of the 18 patients who had a differential white-cell count 17 had an eosinophilia, while of the 76 cases in both outbreaks 39 had differential counts, 38 having an eosinophilia ranging from 64 to 8%.

Incubation Period

The earliest admissions to hospital were on 20 January in Tralee and Killarney, while those patients admitted to hospital after this date had been sick for varying periods. One woman admitted on 26 January had first become ill on 5 January, when she had a rigor and went to bed with nausea, vomiting, anorexia, and pains in her limbs; she also felt weak and was unable to walk because of stiffness. She was the first to become sick, having had an incubation period of six days. The incubation period in trichinosis may last from one day to one month, and its length appears inversely related to the severity of infection (see review by Beck and Beverley-Burton, 1968).

Fifty-five (72%) of the 76 patients had eaten raw pork, almost exclusively as sausages—though it was not possible to incriminate any particular brand. Of these, 37 (77%) were women and 18 (64%) men. While 21 of the 26 cases in Cork were in the city the distribution of cases in Kerry was very wide (see Map). Two or more of these were found in seven households in Kerry, while seven cases occurred in one household of eight—all of whom had eaten raw sausages. The age and sex distribution of the 76 cases is shown in Table II. The youngest patient was aged 3 years and the oldest 70. No death occurred in the Kerry outbreak.



Distribution of cases in Cork and Kerry.

TABLE II.—*Age and Sex Incidence of 76 Cases*

Age:	0–14	15–24	25–44	45–69	70+	Total
Females	8	7	20	12	1	48
Males	7	4	12	5	0	28

Differential Diagnosis.—This covers a wide spectrum from glomerulonephritis to such rare conditions—with pyrexia and eosinophilia—as methyldopa fever (Glontz and Saslaw, 1968), toxocara infestation, and fascioliasis. Other helminthic and allergic diseases as well as causes of pyrexia of unknown origin have to be considered. The association, however, of periorbital oedema, myalgia, pyrexia, and eosinophilia should indicate trichinosis, particularly when combined with the epidemiological evidence of eating raw sausages.

Treatment

No beneficial drug was available for this disease until steroid hormones were introduced. This form of treatment was found highly successful by numerous clinicians (Zaiman *et al.*, 1962; Adamczyk and Osuch, 1961; Forrester *et al.*, 1961; Ozeretskovskaya, 1965; Brown, 1967). Moreover, three patients in the Kerry outbreak responded well to corticosteroids.

Recently the use of thiabendazole in the treatment of trichinosis in rodents and pigs (Campbell, 1961; Campbell and Cuckler, 1962, 1964) and in humans at a dosage of 20–25 mg./kg. twice daily for two to four days (Stone *et al.*, 1964; Kean, 1967) has been equally successful. Though nine patients in Kerry were treated with thiabendazole—two having 50 g. each—its value has not been proved. Experience in Kerry suggests that, as in mice (Lamina and Schoop, 1966), the effect of the drug lessens progressively according to the time interval following initial infection. Perhaps a combination of corticosteroids and thiabendazole might produce better results.

Mode of Transmission

Trichinosis is not common in Ireland or Britain. Van Someren (1937) mentions Cobbold, who quoted Sir Dominic

Corrigan as saying that the disease "was quite common in many parts of Ireland." No other reference to the disease in Ireland was made until 705 cases occurred in a German prisoner-of-war camp in Northern Ireland (Day *et al.*, 1946).

The report by Dr. J. Magner, Cork, on 1 February 1968 of a case of eosinophilia of 35% (4,025/cu. mm.) occurring in one of the domestic staff of a local hospital and a similar one of 46% (8,648/cu. mm.) in Tralee, Co. Kerry, led to an investigation of the position there, though both patients had negative latex trichina slide agglutination tests. The patient in Tralee was not a good witness, but another patient in an adjoining room had periorbital oedema. Similarly, a patient with periorbital oedema was seen near Listowel. Blood was taken from the two patients in Tralee and also the Listowel patient; of these both the Tralee patients had positive trichina tests on 5 February (one previously negative) while the Listowel patient had a negative test which subsequently became positive. The Cork patient had eaten raw sausages and, furthermore, was a native of Kerry, having been home on holiday from 29 December to 2 January. Her trichina test on being repeated was positive. The infestation of the larvae of *Trichinella spiralis* therefore probably occurred at the midpoint of these five days—that is, 31 December 1967. Later 13 other cases—admitted mainly to cottage hospitals—were confirmed, but the bulk of the 50 cases were discovered by epidemiological investigation. Two patients in Tralee had biopsies, both of which were positive, one being confirmed by Dr. Magner, the other by Professor C. Wright and both findings corroborated by Professor G. S. Nelson, London School of Tropical Medicine. Thirty-six of the 50 Kerry patients (72%) admitted eating raw pork, almost exclusively sausages, and these together with the Cork patients total 55 out of 76 (72%).

Discussion

T. spiralis has been reported in at least 65 species of mammal, the real maintenance hosts being carnivores (Nelson, 1968). Direct infections from bears (Rausch *et al.*, 1956; Roselle *et al.*, 1965), wild boar (Gancarz, 1961), bush-pig (Forrester *et al.*, 1961), and other wild carnivores (Nelson *et al.*, 1963) are rare, and most human infections are derived from the domestic pig, which itself can be infected by eating (1) carcasses of infected wild carnivores, (2) infected rats, (3) infected swill, (4) faeces of transport hosts, (5) other pigs' tails.

Is there a true feral cycle in Ireland, where wild carnivores constitute a persistent reservoir of infection which occasionally spills over into the domestic cycle with involvement of pigs or rats? In Britain only one instance of an infected wild carnivore is on record—a red fox at Truro (Oldham and Beresford-Jones, 1957).

Redahan (1967), in Dublin, found no evidence of *T. spiralis* in 1,000 pigs and 32 rats. Schwabe (1964) reported that levels of infection in man and swine were not necessarily good indicators of trichinosis endemicity—for example, in Italy human and swine infections are extremely rare, but the parasite has been found in 33% of 594 foxes examined (Leinati and Marazza, 1959). The parasite was found in 10 out of 212 rats and in 1 out of 58 cats in Limerick (Furnell, 1957). Spink and Augustine (1935) said the infection in pigs and rats had its origin in scraps of trichinous pork, while Gould (1945) asserted that in the U.S.A. and areas where pigs are reared for human consumption trichinosis is maintained as a disease and is disseminated chiefly by the pig, the source of infection being ascribed almost entirely to feeding of uncooked garbage containing scraps of raw trichinous pork. This theory is supported by Most (1965), who showed that the human infection rate in the U.S.A. had dropped from 15 to 20% in 1940 to 4% in 1965. He attributed the downward trend of prevalence and degree of infection with *T. spiralis* in man and pigs to the enactment and enforcement of regulations prohibiting the use of uncooked garbage in swine feed. Legislation exists in Ireland, as in other countries, making it compulsory to boil swill for a minimum period before feeding to pigs. The large pig-breeder complies, but it is impossible to ensure that the small producer always does.

Schnurrenberger *et al.* (1964), in simulated commercial conditions, showed that 5 out of 26 contact pigs were infected with *T. spiralis* apparently by ingesting larvae shed in the faeces of intentionally infected pigs within five days of exposure. Furthermore, workers in Russia and elsewhere have shown that carnivorous birds fed trichinous meat pass cysts in their faeces, which remain infective to mice up to 15 days under ideal conditions (Schwabe, 1964). Pig's tail contains skeletal muscle and may also be contaminated by faeces. The habit of tail chewing (Zimmerman *et al.*, 1962) or coprophagy may therefore contribute to the maintenance of infection among pigs.

The following problems have been raised by these outbreaks.

(1) Is there a true feral cycle in Ireland as exists in Europe, the Arctic, and Africa? The transmission cycle of *T. spiralis* in Ireland remains to be elucidated and the examination of large numbers of animals—for example, foxes, badgers, stoats, etc.—is necessary before we can be sure there is no indigenous cycle among them.

(2) Has the parasite been introduced in infected sausages by travellers from Europe?

(3) In 1967 Irish farmers were complaining about the price of pig feed and said that because of this the margin of profit was insufficient to make pig rearing an attractive economic proposition. This appears to be borne out by the fact that in 1967 the number of pigs killed was the lowest since 1960 (Pigs and Bacon Commission, 1967). Did the economics of pig rearing lead to an increased consumption of swill? Hotels are numerous in Kerry, which is the chief tourist county in Ireland. Furthermore, Cork, Kerry, and Tipperary, where outbreaks have occurred, produce 35% of the total pigs in the country (Pigs and Bacon Commission, 1967).

(4) A feature of many dumps is that innumerable gulls, grey crows, and magpies feed on food thrown on the dumps. Similarly, in some areas pig offal is also thrown on these. A possibility is that these birds act as transport hosts (Britov, 1962). Many Irish farmers allow sows to roam the fields, which, if they eat the faeces of scavenging birds, might become infected through ingestion of encysted larvae in much the same way as cattle are believed to be infected with *Cysticercus bovis* (Silverman and Griffiths, 1955). Furthermore, moisture is thought to be an important factor in sustaining active trichinae in faeces in an external environment (Robinson and Olsen, 1960), and south-west Ireland has the highest rainfall in the country. Pork used in sausages generally consists of inferior meat and much of it is derived from sows. The old sow therefore is the most likely source of infected sausages. With the continued improvement in specificity and sensitivity of serological testing for *T. spiralis* perhaps the day is near when it may be possible to ensure that at least all older pigs are tested before slaughter. Meanwhile adequate cooking, together with education of the public concerning the dangers of eating raw or undercooked pork—especially sausages—is the best protection against trichinosis.

ADDENDUM.—A further sporadic case of trichinosis in Co. Waterford was confirmed in September 1968, and more cases in another area of Ireland were confirmed in December 1968. The danger is that the disease may become endemic.

Thanks are due to the following for their help and co-operation, without which this report would not be possible. In Kerry: Drs. J. Brosnan, J. Coffey, K. Condon, R. Corridan, J. Devine, P. Dunlevy, P. Fuller, J. Gallagher, J. Lawlor, T. McCarthy, M. O'Connor, W. O'Sullivan, W. Prendiville, A. Sheehan,

E. Sheehan, R. Shanahan, and P. Scully. In Cork: Drs. B. Foley, J. Magner, C. Wright, and Mr. P. Flaherty. In Waterford: Drs. K. Hickey, T. Keogh, and J. Walsh. In Limerick: Dr. J. Nash. In London: Professor G. S. Nelson. We wish to thank Professor Z. Kozar, Wroclaw, Poland, for bibliography summaries.

REFERENCES

Adamczyk, J., and Osuch, T. (1961). *Przeglad Epidemiologiczny*, **15**, 399.
Aikawa, J. K. (1966). In *Current Diagnosis*, edited by H. F. Conn, R. J. Clohecy, and R. B. Conn, p. 101. Philadelphia and London, Saunders.
Beck, J. W., and Beverley-Burton, M. (1968). *Helminthological Abstracts*, **37**, 1.
Britov, V. A. (1962). *Zoologicheskiĭ Zhurnal*, **41**, 776.
Brown, H. W. (1967). In *Cecil-Loeb Textbook of Medicine*, edited by P. B. Beeson, and W. McDermott, 12th ed. Philadelphia and London, Saunders.
Campbell, W. C. (1961). *Journal of Parasitology*, **47**, No. 4, Section 2, p. 37.
Campbell, W. C., and Cuckler, A. C. (1962). *Journal of Parasitology*, **48**, No. 2, p. 28.
Campbell, W. C., and Cuckler, A. C. (1964). *Journal of Parasitology*, **50**, 481.
Corridan, J. P., and O'Meara, P. B. (1968). *Irish Journal of Medical Science*, 7th series, **1**, 109.
Day, C. L., Wood, E. A., and Lane, W. F. (1946). *Journal of the Royal Army Medical Corps*, **86**, 58.
Drury, M. I. (1957). *Irish Journal of Medical Science*, 6th series, **7**, 84.
Forrester, A. T. T., Nelson, G. S., and Sander, G. (1961). *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **55**, 503.
Furnell, M. J. G. (1957). In *Annual Report of the Medical Research Council of Ireland*.
Gancarz, Z. (1961). *Przeglad Epidemiologiczny*, **15**, 1.
Glontz, G. E., and Saslaw, S. (1968). *Archives of Internal Medicine*, **122**, 445.
Gould, S. E. (1945). *Trichinosis*. Springfield, Illinois, Thomas.
Hall, M. C. (1937). *Public Health Reports*, **52**, 539.
Innella, F., and Redner, W. J. (1959). *Journal of the American Medical Association*, **171**, 885.
Kean, B. H. (1967). *Annals of Internal Medicine*, **67**, 461.
Lamina, J., and Schoop, G. (1966). *Berliner und Münchener tierärztliche Wochenschrift*, **79**, 34.
Leinati, L., and Marazza, V. (1959). *Clinica Veterinaria (Milano)*, **82**, 1.
McGill, D. A. (1957). *Guy's Hospital Reports*, **106**, 92.
Most, H. (1965). *Journal of the American Medical Association*, **193**, 871.
Nash, J., Kidney, J. G., Furnell, M. J. G., and O'Meara, P. B. (1957). *Journal of the Irish Medical Association*, **40**, 74.
Nelson, G. S. (1968). In *Some Diseases of Animals Communicable to Man in Britain*, edited by O. Graham-Jones, p. 77. Oxford, Pergamon Press.
Nelson, G. S., Guggisberg, C. W. A., and Mukundi, J. (1963). *Annals of Tropical Medicine and Parasitology*, **57**, 332.
Norman, L., and Kagan, I. G. (1963). *Public Health Reports*, **78**, 227.
Oldham, J. N., and Beresford-Jones, W. P. (1957). *British Veterinary Journal*, **113**, 34.
Ozeretskovskaya, N. N. (1965). *Meditsinskaya Parazitologiya i Parazitarnye Bolezni*, **34**, 379.
Pigs and Bacon Commission, Ireland (1967). Annual Report.
Rausch, R., Babero, B. B., Rausch, R. V., and Schiller, E. L. (1956). *Journal of Parasitology*, **42**, 259.
Redahan, E. (1967). *Irish Veterinary Journal*, **21**, 168.
Robinson, H. A., and Olsen, O. W. (1960). *Journal of Parasitology*, **46**, 589.
Roselle, H. A., Schwartz, D. T., and Geer, F. G. (1965). *New England Journal of Medicine*, **272**, 304.
Schnurrenberger, P. R., Masterson, R. A., Suessenguth, H., and Bashe, W. J. jun. (1964). *American Journal of Veterinary Research*, **25**, 174.
Schwabe, C. W. (1964). *Veterinary Medicine and Human Health*. Baltimore, Williams and Wilkins.
Semple, A. B., Davies, J. B. M., Kershaw, W. E., and St. Hill, C. A. (1954). *British Medical Journal*, **1**, 1002.
Silverman, P. H., and Griffiths, R. B. (1955). *Annals of Tropical Medicine and Parasitology*, **49**, 436.
Spink, W. W., and Augustine, D. L. (1935). *New England Journal of Medicine*, **213**, 527.
Stone, O. J., Stone, C. T., and Mullins, J. F. (1964). *Journal of the American Medical Association*, **187**, 536.
Van Someren, V. D. (1937). *British Medical Journal*, **2**, 1162.
Zaiman, H., Ingalls, J. W., jun., and Villaverde, H. (1962). *Experimental Parasitology*, **12**, 418.
Zimmerman, W. J., Hubbard, E. D., Schwarte, L. H., and Biester, H. E. (1962). *Cornell Veterinarian*, **52**, 156.

Preliminary Evaluation of Four Oral Contraceptives Containing only Progestogens

ELEANOR MEARS,* M.B., CH.B.; M. P. VESSEY,† M.B., B.S.; LIDIJA ANDOLŠEK,‡ M.D.; ANTONIJA OVEN‡

British Medical Journal, 1969, **2**, 730–734

Summary: One hundred and seventy-five women took part in a comparative clinical trial of four progestogen-only oral contraceptives and were followed for either a year or until treatment was discontinued. Megestrol acetate 0·25 mg. was found to be a very ineffective contraceptive, 21 out of 43 women becoming pregnant. One, three, and four pregnancies occurred during treatment with norethisterone acetate 0·3 mg., norgestrel 0·05 mg., and chlormadinone 0·5 mg., respectively, corresponding to pregnancy rates of 4, 9, and 12 per 100 woman-years of use.

All three effective progestogens were very much less acceptable than modern low-dose combined oral contraceptives. Discontinuation of treatment for medical reasons (particularly menstrual disturbances) during the course of only one year affected 24% receiving norethisterone acetate, 38% receiving norgestrel, and 46% receiving chlormadinone.

* 111 Harley Street, London W.1.
† Member, Scientific Staff, Medical Research Council's Statistical Research Unit, London W.C.1.
‡ Family Planning Institute, Ljubljana, Yugoslavia.

Introduction

A small dose of an orally active progestogen administered every day throughout the menstrual cycle exerts a pronounced antifertility effect which so far has not been adequately explained. Ovulation is certainly not regularly inhibited by such medication, and changes in the endometrial morphology seem to be minor and variable. Alterations in the physicochemical properties of the cervical mucus occur fairly consistently, but are thought to be insufficient to account entirely for the contraceptive action.

Previous laboratory and clinical experience with the available orally active progestogens has shown that each has a different dose-related range of hormonal activity with varying effects on the ovaries, Fallopian tubes, uterus, cervix, and vagina. The problem is to find a dose of some progestogen, if such exists, which will prevent conception without interfering with the menstrual cycle and with the endogenous hormonal pattern. Rudel *et al.* (1965) considered the most promising substances to be the 17α-hydroxyprogestogens, which do not inhibit ovulation in the doses at present used for contraception. These substances have strong progestational