HORMONAL PREGNANCY TESTS:
A possible association with congenital abnormalities

COMMITTEE ON SAFETY OF MEDICINES

A number of studies have shown a possible association between taking mixtures of an oestrogen and a progestogen as a means of diagnosing pregnancy and an increased incidence of congenital abnormalities.

The Committee on Safety of Medicines wish to draw attention to these studies and to the preliminary results of their own case-control study. The early results suggest that a relatively greater proportion of mothers of abnormal babies had been tested in this way. A letter describing these preliminary results was published in the British Medical Journal on April 26 1975. (Greenberg, et al, ii, 191). The Committee will present their further conclusions later in the year, when their study is completed.

On the present evidence, the Committee believe that it is possible that the use of these preparations for the diagnosis of pregnancy could on occasion lead to abnormalities in the foetus. There are other means of diagnosing pregnancy which do not require the administration of hormones, and the Committee consider that in view of this possible hazard this method should not now normally be used.

As the data began to accumulate it was felt advisable to inform the companies known to be concerned and it was ascertained either that they had ceased to promote the products for this use, or that the product had been removed from the market. With this further evidence of this possible hazard, the Committee have advised the Health Departments that measures should be taken to ensure that this indication is not included in licences for such products and to require the insertion in all promotional literature of a warning about this possible hazard in pregnancy.

As far as is known the hormone preparations which have been, at some time, used or recommended for this purpose are:

Amenorone	Norlestrin	Paralut
Amenorone Forte	Norlutin A	Pregornot
Disecron	Norone	Primodos
Menstrogen	Orasecron	Secrodyl

Some of these products are no longer on the market, whilst others will continue to be marketed for the treatment of a variety of conditions in women who are not pregnant.

ADVERSE REACTIONS SERIES

NO 13
JUNE 1975

Committee on Safety of Medicines,
Finsbury Square House,
33/37A Finsbury Square,
LONDON EC2A 1PP.

Telephone: 01-638 8020

٩

Dear Karl Murphy,

Re: Norethisterone our ref: ICE 09/0672

Thank you for your recent enquiry to the Medicines and Healthcare products Regulatory Agency (MHRA).

According to our licensing records, products containing the active substance norethisterone were contraindicated (not recommended for use) in pregnant women at least as far back as the early 1970's. The medicines licensing began in 1971 so we would not have any information on the status of norethisterone before this time.

Yours sincerely

Information Centre
MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY
LONDON SW8 5NQ

Telephone +44 20 - 7084 2000
Facsimile +44 20 - 7084 2353
Home Page

Please address all E-mail correspondence to: **info@mhra.gsi.gov.uk**

10

EP Drug

High-dose estrogen-progesterone (EP) combination drugs contain the same female sex hormones as the combined oral contraceptive pill but at a higher level. These drugs were used in 1950s as a treatment for missed periods since they were thought to start menstruation in women whose periods were delayed and who were not pregnant. A woman whose periods did not start after taking EP drugs was presumed to be pregnant, and hence EP drugs were used for pregnancy testing. But because the drug could apparently bring on menstruation, EP drugs were misused to induce abortion. Although no pharmaceutical company has ever claimed that these drugs will induce abortion, there was evidence in India that they were prescribed by doctors for this purpose and were also sold over the counter. About 20 years later research uncovered evidence that the EP drugs were unreliable as pregnancy tests and ineffective as treatment for missed periods. In fact evidence showed that the drugs were associated with birth defects. Those women who used this drug for pregnancy testing and continued with their pregnancy exposed their unborn babies to the possibility of birth defects. Those women who took the drug to induce abortion but did not abort, also ran the same risk. Many countries began to withdraw this drug since 1970. In India the drug was used for a variety of disorders and by 1982, an estimated 180,000 were using the drug each year. The Indian health and consumer groups launched a campaign for the withdrawal of this drug and as a result a warning was added in the drug information insert," Not to be used for pregnancy test and suspected cases of pregnancy". In June 1992, the Drug Controller of India banned the manufacture of all EP formulations effective from 31 December 1982, and its sale from 30 June 1983. The ban was severely criticised because though it was considered hazardous enough to be banned, yet it was allowed to be sold for another six months simply so the stocks would finish. However two pharmaceutical companies Unichem and Nicholas contested the ban. Infar, the Indian subsidiary of the Dutch pharmaceutical company, Organon, which is not allowed to manufacture and sell the product in its home country, filed a petition against the ban. Their arguments covered various aspects of the ban: the legalities, drug misuse, hazards and medical details. As a result in January 1983, a stay order against the ban and a two-year extension of the product license was granted by the Calcutta and Bombay High Courts on legal technicalities. The ban was thus effectively stalled by the stay order. This meant that till the case came up for trial, the hazardous drugs could be manufactured and sold in the country. Appalled by this decision, various health and consumer organisations continued the campaign (see Case study of "A Successful Campaign" in Chapter 5) and after five years of relentless struggle, they succeeded when in 1988, the Indian government banned the manufacture and sale of high-dose combination of EP "containing per tablet estrogen content of more than 50 micrograms and of progesterone content of more than 30 milligrams". This judgment is particularly welcome when safer alternatives and non-drug methods for pregnancy testing are available in the country.

referred to a one-man commission whose report has not seen the light of day yet.)

The prime technique adopted by the Tamil Nadu government to harass the activists and office-bearers of TNGCTA is to transfer them from where they are active. During the beginning of the current academic session, the government has transferred 252 teachers, most of whom were activists or office-bearers of TNGCTA. In Madras city alone, thirty-five teacher activists, including three zonal office-bearers, have been transferred.

The case of Vasanthi Devi, professor of history at the Government Arts College for Women, Dindigul, is a graphic case of how the government uses its power to transfer teachers as an instrument of victimisation. Vasanthi Devi, the joint secretary of TNGCTA, functioned as the convenor of JACTTEA in Dindigul during the 1985 agitation and courted arrest. As a price for active participation in the agitation she was transferred from Dindigul to Kumbakonam. On a writ petition filed by her, the Madras High Court decreed that the transfer was mala-fide. However, the government refused to implement the judgment and the high court once again issued an interim order to allow her to rejoin her post in her original college. The government appealed to a division bench of the High Court and subsequently to the Supreme Court to get the judgment reversed, but in vain. The point to be underlined is that the Tamil Nadu government can go all the way to the Supreme Court to harass a single teacher.

The government uses many other methods as well to break the teachers' movement: (a) The blacklegs are given certain extra benefits over teachers who participate in agitations. For instance, the government granted eleven extra days of earned leave to the teachers who reported to duty during the JACTTEA agitation. (b) The government has promoted a loyalists' association named the Tamil Nadu Government Collegiate Teachers Welfare Association to break the teachers' movement. Though the association has hardly two hundred members and is unrecognised, the government holds talks with it and refuses to meet the representatives of the recognised teachers' associations having a membership of over 12,000 teachers. (c) Section 41 of the City Police Act is perennially kept in force in Madras city to prevent the teachers and other labouring classes from conducting any peaceful demonstration or hunger strike.

It is not only the Tamil Nadu government which intimidates the teachers, but the private college managements also. We shall cite two cases to illustrate this. First, Gugananda Swamiji, the secretary and correspondent of Vivekananda College near Madurai, led a band of twenty lathi-wielding goondas and set them on the striking teachers, injuring two of them. Secondly, the management of the Sir Theagaraya College in Madras has already issued show-cause notice to 41 striking teachers seeking explanation why they should not be suspended. The management has isolated two of the active members of the teachers' movement—V Loganathan, professor of economics and former president of the AUT, and K Balakrishnan, professor of Tamil who happens to be the brother of DMK general secretary K Anbazhagan—and charged them in show-cause notice with obstructing students from attending classes.

Despite this atmosphere of intimidation by both the government and the private college managements, the on-going teachers' agitation has expanded its active support base. Significantly, most of the new entrants to the movement come from minority-run private colleges which are only too well known for misusing their minority status to victimise the dissenting teachers.

Almost all the teachers of Loyola College in Madras, whose Jesuit management has a long history of suppressing ruthlessly any dissent from teachers, have joined the strike. After a week of the strike, the principal of the college convened a staff meeting and asked the teachers to report back for duty. But the teachers refused. Similar is the case with Stella Maris College in Madras. Twentyfive women teachers of Stella Maris College, which is a Roman Catholic institution with the management having a firm control over the staff, have joined the present strike. The Stella Maris College is known for its non-participation in the teachers' movement in the past. Eightyeight teachers of St Joseph's College, Tiruchi, which is again a minority institution having only twentytwo AUT members, have joined the strike. Jesuit fathers of the college led the procession of teachers in Tiruchi town. These teachers have joined the agitation at the risk of extreme consequences.

The spirit of the striking teachers could be gauged from the Negro Spiritual sung with gusto during a hunger strike in front of the Directorate of Collegiate Education by the women teachers from Stella Maris College who have joined the strike for the first time:

> We shall overcome, we shall overcome
> Deep in my heart, I do believe
> We shall overcome some day.

EP Drugs Inquiry: Why Is Industry Upset?

Arun Bal

For the first time the drug industry has had to defend one of its products at a public inquiry. It perceives the inquiry as a trend which threatens its hitherto unchallenged hold over the consumers as well as the medical profession. This is why it has used every possible tactic—deceit, falsehood, and even the threat of violence—to obstruct the public hearings and oppose the ban. The Bombay hearing provided ample evidence of all this.

THE high dose FP drugs campaign and the public inquiry ordered by the Supreme Court mark a watershed in the rational drug therapy movement in more than one sense. The public inquiry was the outcome of the sustained efforts by the consumer activists and women's groups over a period of more than two years. This inquiry was an education in itself, a very vital and important one, for the activists. It revealed the inherent strengths and weaknesses of the rational drug therapy campaigns. A retrospective of the events connected with the inquiry reveal some fascinating aspect of the inter-relationship between the industry, government and the drug activists.

High dose FP drugs were banned by the Drug Controller of India (DCI) in 1983 in a rare display of rationality, courage and clarity. However the DCI had, apparently, underestimated the diabolical scheming capabilities of the industry. The companies, Unichem and Organon as a fair move in the long-term strategy to frustrate the DCI's efforts obtained stay orders at various high courts across the country. These injunctions remained operative due to the unfathomable inactivity of the DCI's office. The companies merrily went on producing the drug. Ultimately, it was left to the consumer activists to take the initiative and move to the Supreme Court. The order of Supreme Court directing the DCI to hold a public inquiry in order to decide whether FP drugs should be banned has bared the unsavoury aspect of the industry to the

EP Drugs Public Inquiry
Landmark Event Turned into a Charade

Padma Prakash

In the first judicial order of its kind, the Supreme Court in November 1986 directed the Drugs Controller to conduct a public inquiry to determine whether the sale and manufacture of EP drugs should be banned. Unfortunately, today at the end of the public hearings, there is little reason to believe that the inquiry has been impartial and unbiased or that it has provided adequate opportunity for the public to participate in decision-making.

LAST November the Supreme Court issued a momentous edict. It directed the Drug Controller of India to conduct a public inquiry to determine whether the sale and manufacture of high dose estrogen progesterone (EP) drugs should be banned. This is the first time that a public inquiry on a medical issue has been ordered by the court. It implies a recognition on the part of the court that ordinary citizens of the land have a right to participate in making decisions on matters which affect them, even when these matters are of a scientific and technical nature.

Unfortunately, today after the EP public hearings have all been concluded, there is little reason to believe that the inquiry has been either impartial and unbiased or that it has provided adequate opportunity for the public to participate in decision-making. In fact it has turned out to be a farce. The very concept of the public inquiry which is meant to ensure that the basic principles of natural justice would apply to those who are adversely affected has been distorted.

The Background

High dose EP drugs were first marketed in India in the 60s. By 1967 enough evidence had accumulated all over the world to show that its use was associated with congenital abnormalities. Several countries either banned the drug or persuaded the manufacturers to withdraw it from the market or restricted its use only for gynaecological problems. In 1975 the WHO concluded that the drug should not be used for pregnancy testing. Following this the Drug Controller of India (DCI) notified manufacturers that these drugs were not to be promoted for use as a pregnancy test except when the woman wanted an abortion if her pregnancy was confirmed by the test.

In March 1982 the DCI made it mandatory for manufacturers to print a warning against the use of EP drugs in pregnancy on the drug packets. By June the same year on the advice of the Indian Council of Medical Research (ICMR) the sale and manufacture of these drugs were banned. Three reasons were cited to justify the ban: (1) That it had been banned in several countries; (2) the drugs were being extensively misused; and (3) there were other safer substitutes available. Curiously, however, the DCI allowed the sale of the drug for a period of one year and its manufacture for six months.

Promptly two manufacturers, Unichem Laboratories and Nicholas challenged the order in the Bombay High Court and later Organon—now Infar (India) Ltd—filed a similar writ petition in the Calcutta High Court. The companies pointed out that, firstly, the drug could not possibly be that dangerous since the DCI had after all allowed its sale and, secondly, even if it were, the Drugs and Cosmetics Act did not confer on the DCI the powers to ban a drug. By January 1983, because of these legal loopholes, the manufacturers had obtained a stay order on the ban and were even granted a two-year extension of their manufacturing licenses.

The amendment to the Drugs and Cosmetics Act empowering the government to ban the import and manufacture of drugs came into force in February 1983. And in April Vincent Panikulangara, an advocate from Kerala, filed a writ petition in the Supreme Court seeking directions "for banning the import, manufacture, sale and distribution of such drugs which have been recommended for banning by the Drugs Consultative Committee". High dose EP drugs were included in the petition. In July 1983 the DCI issued a gazette notification banning the 22 fixed dose combination drugs which had been recommended for banning by the DCC. Surprisingly, EP drugs found no mention in the list—on the plea that the case was in court! Panikulangara's petition was amended in November to take note of the ban order and to seek the implementation of the order. The drug industry once again challenged the order on the grounds that objective criteria were lacking for such a ban and the provisions of the amendment Act remained largely inoperative because of injunctions in several high courts.

This is how the matter stood for three years. High dose EP drugs continued to be manufactured and sold despite an order banning them because of legal-technical problems. Not until November 1986 did the Panikulangara writ petition come alive again. On the twelfth of that month the then chief justice R S Pathak and justice Ranganath Mishra issued a stern order to the government of India asking it to reply to the petition and seeking to know the status of the ban ratification and why the state drug control authorities had not implemented the ban orders. It also took a dim view of the lackadaisical attitude of the "concerned department" of the central government and remarked that "for some inexplicable reason [it] is not interested in the disposal of the writ petition, though the writ petition . . . is intended to safeguard and protect unsuspecting public against drugs . . . banned in the developed countries but which are sought to be dumped on third world countries". Neither, it noted, had the Indian Council of Medical Research or "the drug controllers of all the states in India except the drug controller of the state of Kerala" shown any eagerness to assist the court in arriving at a decision.

And yet barely a fortnight later the court announced that it had entrusted the DCI, an organisation of the "indifferent" central government, with the task of holding a public inquiry to decide on the fate of EP drugs. The court thus chose to reopen a decision which had been taken on sound medical grounds on the recommendation of the ICMR. As Indira Jaising, the well known Bombay lawyer pointed out, it is this decision which in the first place should be questioned. While the institution of a public inquiry is no doubt to be welcomed, was the basis on which such a decision was made correct? Moreover, by allowing a six-month time limit for the DCI to conduct the inquiry and arrive at a decision without effecting an interim ban on the sale of the drug, it has permitted the continued exposure of thousands of women to a drug which has been shown to be hazardous and has been banned in so many countries.

A Charade

The EP public inquiry would have been a landmark event with the full and equal participation of all concerned. Instead it rapidly turned into a charade, from the very beginning. For one thing the court order was a bare directive with hardly any stipulations about the manner in which the inquiry should be conducted—notice of the inquiry was to be given to the two companies concerned, Unichem and Infar as well as the petitioners, it was to be