only one such case has been discovered." It appears that in this case vaccination has not given enough resistance because of deficient power of reaction. Frappier, of Montreal, hopes in the course of the next few years to have every child in the province of Quebec vaccinated with B.C.G. vaccine.

B.C.G. vaccination has been criticized and subjected to condemnation largely as a result of unfortunate experiences which can be eliminated by the observance of better technique in the preparation of the vaccine and its administration. Complications of the inoculation undoubtedly arise, but they can be avoided by proper precautions. Wilson (1947) has been critical of the suggestion that the practice should be adopted in this country, and has been replied to by Wallgren (1948). It would seem only fair that a scientific investigation of its efficiency in this country should be carried out with proper controls before embarking upon a national venture which by its biological nature will be damned outright by a section of the community.

Streptomycin

Streptomycin seems to have some control over the progress of tuberculosis in that the original experiments on guinea-pigs proved that the drug would arrest and even partially eradicate well-established tuberculosis in that animal. Hinshaw and Feldman (1945) recorded a favourable response in two-thirds of 75 cases, in some a clinical cure being recorded. Apart from a few unpleasant reactions depending upon dosage, impurities in the preparation, and idiosyncrasy, there is the disadvantage (and it is a disquieting one) that some types of tubercle bacilli are resistant to streptomycin. It would appear that these resistant strains, freed from the dominant restraint of the previously active ones, may infect other individuals and multiply in spite of streptomycin administration and account for much of the deterioration of cases under treatment after the initial improvement (M.R.C., 1948). There is the further consideration that a resistant strain can initiate the disease in other individuals and account for the widespread dissemination of the disease in a form for which streptomycin is innocuous.

In miliary tuberculosis a favourable response is obtained in a number of cases, but post-mortem examinations of fatal cases of tuberculous meningitis do not provide any histological evidence that the tuberculoma has been influenced by the drug; the associated meningeal exudate, however, may show considerable organization and thus account for the clinical improvement. There is a suggestion of a field of usefulness for streptomycin in primary infections, but it will be necessary to review the evidence when an extended trial has been made and a critical review is possible.

Conclusion

I have now completed my task within the limits of time and my competence. I shall not have failed, however, if I have focused attention upon some of the practical aspects of a common disease in infants and children, a disease which carries a heavy responsibility for death, sickness, and incapacity. If I began at the beginning it was because, as Aristotle said, "He who sees things from their beginning will have the finest view of them." If we study and understand tuberculosis in all its aspects in the young we will appreciate all the better the disease in the adult; so that nothing is lost, but perhaps much may be gained, by this approach. By concentrated effort in the preventive field and the use of all available facilities for diagnosis and treatment we can look forward with more hope for its eventual eradication.

REFERENCES

- Asserson, M. A. (1927). *Amer. Rev. Tuberc.*, **16**, 359.
 Barsby, B. (1941). *Lancet*, **1**, 627.
 Blacklock, J. W. S. (1947). *British Medical Journal*, **1**, 708.
 Bledisloe, Lord (1948). *The Times*, Oct. 30, p. 5.
 Burrell, L. S. T. (1933). *Med. Pr.*, **187**, 20.
 Curie, Eve (1938). *Madame Curie*. Heinemann, London.
 Eliasberg, H., and Neuland, W. (1920). *Jhrb. Kinderheilk.*, **93**, 88.
 Ghon, A. (1912). *Der primäre Lungenherd bei der Tuberkulose der Kinder*. Berlin.
 Hinshaw, H. C., and Feldman, W. H. (1945). *Proc. Mayo Clin.*, **20**, 313.
 Joint Tuberculosis Council (1948). Report of Children's Committee.
 Kaye, G. G. (1935). *British Medical Journal*, **1**, 694.
 Lemaire, H. (1925). *Rev. Tuberc.*, **6**, 228.
 McMurray, J. (1944). *Arch. Dis. Childh.*, **19**, 87.
 McNeil, C. (1929). *British Medical Journal*, **2**, 657.
 Malmros, H. (1948). *Ibid.*, **1**, 1129.
 Medical Research Council (1948). *Ibid.*, **2**, 769.
 Myers, J. A., and Harrington, F. E. (1934). *J. Amer. med. Ass.*, **103**, 1534.
 Nassau, E., and Zweig, H. (1925). *Z. Kinderheilk.*, **39**, 484.
 Newsholme, A. (1926). *Lancet*, **1**, 1022.
 Parrot (1876). *C. R. Soc. Biol., Paris*, **28**, 308.
 Wallgren, A. (1948). *British Medical Journal*, **1**, 1126.
 — and Lundblom, A. (1935). *Nord. med. Tidskr.*, **10**, 1699.
 Wilson, G. S. (1947). *British Medical Journal*, **2**, 855.

THE EFFECT OF ENDOCRINES ON FIBRO-ADENOSIS

BY

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A clinic for the investigation and treatment of the painful nodular breast was established at Guy's Hospital in 1937, and except during the years 1941–5 it has been functioning weekly since that date. At different times I have been assisted in the running of the clinic by various workers, but my thanks are due particularly to Dr. P. M. F. Bishop, endocrinologist to the hospital, who launched the project with me, and whose advice has always been available. All expenses incurred in the investigations have been defrayed by an annual grant from the British Empire Cancer Campaign.

I originally set out to investigate the effect of endocrine preparations on the disease which we now call fibro-adenosis, defined as "a painful or nodular condition of the breast not due to new growth, bacterial inflammation, or fat necrosis" (Atkins, 1938). As this part of the investigation is complete I am submitting a report of the findings. The clinic is at present devoted to a clinico-pathological investigation into the effect of endocrines on established cancer of the breast and to following up the now considerable series of cases of fibro-adenosis.

A report has already been given of the early work in connexion with the administration of oestrogens, and androgens in the form of injections of testosterone propionate (Atkins, 1940), but a brief recapitulation of our findings may not be out of place.

Bearing in mind the importance of the psychological aspect of this condition and the subjective nature of many of the manifestations, together with the absence of any absolute standards of such objective phenomena as "nodularity," we were careful to control our results by submitting a parallel series of cases to a course of injections of sterile olive oil if the subsequent therapeutic agent to be investigated was to be injected, and to a course of chalk pills if the agent was to be taken by mouth.

In nearly every case a random sample of breast tissue was taken by biopsy from that part of the breast where the disease was judged to be most advanced, and submitted to histological examination. A second sample was taken at the conclusion of the treatment and at a corresponding

period in the menstrual cycle. In this way we were able to assess the clinical effect of the substance being investigated and, because the pieces of tissue removed for section were only random samples, to a limited extent the histological changes.

Oestrogens

Thirty-three patients were given oestrogen therapy. They received at least 80 mg. of oestradiol benzoate by injection in four weeks or 280 mg. of stilboestrol by mouth in eight weeks; 19 of these patients had much higher doses.

Our conclusions, based on a clinical follow-up of these 33 cases and set out in detail in the above paper (Atkins, 1940), were that oestrogens were harmful if given in doses large enough to be effective, and that the larger the dose the more harmful was the effect. We formed the impression that histologically the fibroblastic reaction, the epitheliosis, and the adenosis all tended to increase.

Androgens

Thirty-four patients received injections of testosterone propionate; 22 of them had at least 400 mg. in four weeks, and many received considerably higher doses.

It was found that the majority of the patients benefited temporarily by these injections but tended to relapse some weeks after the cessation of treatment. Further, eight of these patients suffered hirsuties, amenorrhoea, and deepening of the voice, and two of the eight had received only small doses of testosterone propionate.

One patient receiving large doses (1,200 mg. in six weeks) developed a carcinoma of the breast at the site of the original fibro-adenosis one year later, the only case at that time to develop carcinoma following fibro-adenosis.

Histologically some of the features of fibro-adenosis seemed less advanced after androgen therapy than before, but of this we were uncertain; and the acid test of sorting the pairs of slides with the labels obscured into "before androgen" specimens and "after androgen" specimens was equivocal. It was concluded, therefore, that the risks entailed in this form of therapy did not justify the temporary relief obtained.

It was at this stage that the war interrupted the investigations. They were resumed in 1946, when it was decided to investigate other methods of androgen administration, using the same techniques of clinical and histological control as those described above. The effects of administering androgens by mouth, by inunction, and by implantation were therefore explored, with the following results.

Twelve patients received 15 mg. of methyl testosterone by mouth daily for two months: seven were relieved of their symptoms for an average of seven months, the longest being eleven months; one was relieved of her symptoms only while the tablets were being taken, the symptoms returning immediately afterwards; three had no relief from their symptoms; and one did not attend the clinic again and cannot be traced.

Nineteen patients received 400 mg. of testosterone propionate in the form of "neo-hombreol" ointment applied to the breast in divided doses daily for a period of one month. Six of these were relieved for an average period of four and a half months after treatment stopped, the longest being nine months; seven said that the pain was relieved while the ointment was being used, but recurred as soon as the treatment stopped; and six said that there was no relief of symptoms.

Eleven patients received 100 mg. of testosterone implanted deep into the breast tissue at the time that the first biopsy was performed. Of these, four were relieved of their symptoms for 1, 2, 3, and 6 months, followed by a relapse; two showed slight improvement for the follow-up period (4 and 5 months); four were not relieved of their symptoms (one extruded the tablet after three months); and one complained that the symptoms were made worse.

The impression gained was that the patients receiving androgen therapy enjoyed a real though slight and only temporary improvement in their symptoms as a result of the androgen absorbed.

None of the cases receiving androgen in the above doses by mouth, by inunction, or by implantation developed symptoms or signs of masculinization, nor in this series was there any constant difference in the histological picture between the original biopsy specimen and the specimen taken after the administration of the androgen. It will be recalled that the histological changes effected by large doses of testosterone propionate by injection were not convincing, and this finding is directly at variance with that of Pricolo and Goisis (1946), who claimed substantial changes in the histological picture as the result of administering androgens in smaller doses than we had been using in our first series.

It must be emphasized that the only crucial test, where random samples of the breast are taken for biopsy, is for an independent histologist to examine the pairs of slides, each of which is given a code number, and to succeed in diagnosing these slides correctly as representing tissue before and after androgen therapy in a significant number of cases. The possibility that androgen therapy modifies the histological picture of the breast is not denied, but the extent to which it does so is far less than the paper cited above would lead one to expect.

Degrees of nodularity are not susceptible to exact measurement, but undoubtedly in a few cases the nodularity was less after androgen therapy. Before claiming these few findings as evidence of the effect of androgen therapy, however, it must be remembered that in a substantial proportion of cases of fibro-adenosis natural remissions occur. Furthermore, the feel of the breast in the majority of our cases receiving androgen therapy did not alter.

Discussion

In a high proportion of cases oestrogen therapy makes the symptoms and signs of fibro-adenosis worse and advances the histological changes characteristic of the disease.

In a substantial proportion of cases androgen therapy causes temporary improvement in the symptoms of fibro-adenosis. The safest, most effective, and most convenient way of administering androgens is in doses of 15 mg. of methyl testosterone by mouth daily for two months. Androgen therapy has less, if any, effect on the nodularity and no constant detectable effect on the histological picture.

My view is, nevertheless, that androgen therapy is not worth while in the disease fibro-adenosis. The pain, divorced from the apprehension, is rarely excessive, and the vast majority of patients, relieved justifiably of their apprehension, forget it. Where the pain is "intolerable" or "agonizing" it is not relieved even temporarily by androgens, and my experience during the early days of the clinic of removing in desperation both breasts in six cases so complaining, after everything else had been tried, has led me to believe that it is doubtful whether the pain is due to fibro-adenosis. Four of these patients still complain of "intolerable" or "agonizing" pain where the breasts were, and the remaining two have transferred their agony to other sites.

It is not justifiable to administer androgen therapy to these patients in the hope that this will prevent the onset of cancer (Loeser, 1938), as the case cited above exemplifies. It is not proposed here to enter into the question of the liability to malignant change in this disease, as this subject,

together with a full discussion of the pathology, significance, and natural history of fibro-adenosis, is to be made the subject of a further report elsewhere. Experience in the clinic has, however, led me to believe that, whatever views are taken about the possible precancerous nature of fibro-adenosis, these patients should be seen by their medical attendant at least every six months. I had thought originally that these continuous visits to the doctor might serve to emphasize and fix the fear of cancer in the patient's mind, but I find in practice that the effect is quite otherwise. Psychologically the patient is able to transfer the whole burden of responsibility to the shoulders of the medical attendant, where it should properly rest, and in the meantime cease worrying, in the knowledge that, in the remote chance of anything sinister developing, it will be dealt with without delay.

If the view is accepted that breast pain is due to the stimulation of nociceptive nerve endings by adjacent fibroblasts, and that these fibroblasts are elaborated in response to epithelial changes in the ducts, as many of the clinical features suggest (Atkins, 1939), then it is easy to see why androgens can have only a limited and temporary effect. Such effect as they do have is presumably the inhibition of oestrogenically stimulated epithelial growth, but without any modification of pre-existing epithelium, hence the absence of histological change. So long as the androgen is being administered inhibition will continue; but at a variable period after it is withheld the natural hormonal balance of the individual is resumed, and oestrogen-stimulated epithelium appears in the ducts with a consequent reactionary fibrosis and recurrence of symptoms.

There is really nothing that we know of at present which permanently modifies these processes apart from pregnancy and lactation, which revolutionize the physiological pattern, and the passage of time. Particularly about the menopause, fibroblasts disappear from the breast (there being no longer any considerable epithelial activity for them to restrain, if we care to think of it in that way) and they fulfil their natural function of being converted into inert collagen fibrils. When this happens the pain ceases. The administration of endocrines in an attempt to modify fibroblastic pain of this sort is not unlike the prescription of penicillin for an inflamed keloid scar—it may affect a little something, but does not get to the root of the trouble and is scarcely worth while.

Like fibroblastic pain in general, the pain of fibro-adenosis, which often varies with the weather, can frequently be relieved temporarily by radiant heat. X-ray treatment, on the other hand, is disappointing, and it cannot be denied that the most efficacious treatment is still that of Sir Astley Cooper (1829): a scrupulously careful examination, a confident diagnosis, a justifiable reassurance, and "the return of the patient with delighted affection to her family."

Conclusions

The effect of oestrogens on fibro-adenosis is harmful.

The effect of androgens may be temporarily beneficial, but it is not sufficiently so to encourage the use of these substances therapeutically in this disease.

The histological effect of androgens in therapeutic doses on breasts in cases of fibro-adenosis is inconstant.

REFERENCES

- Atkins, H. J. B. (1938). *Lancet*, **1**, 707.
 — (1939). *British Medical Journal*, **1**, 866.
 — (1940). *Lancet*, **2**, 411.
 Cooper, Sir Astley (1829). *Illustrations of the Diseases of the Breast*. London.
 Loeser, A. A. (1938). *British Medical Journal*, **2**, 319.
 Pricolo, V., and Goisis, M. (1946). *Tumori Milano*, **20**, 175.

CURARE-MODIFIED ELECTRIC CONVULSION THERAPY IN CASES WITH PHYSICAL DISEASE

BY

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Many mental patients are denied the benefits of electric convulsion therapy (E.C.T.) because of physical contraindications. The purpose of this article is to show that, with few exceptions, even the most severe physical disability should not debar such patients from the use of this method. We here report the results obtained at Shenley Hospital in 50 cases in which the physical condition of the patients rendered them unsuitable for ordinary E.C.T., but in which, nevertheless, this treatment, modified by curare, was used.

Review of Literature

Textbooks contain few detailed instructions regarding contraindications to E.C.T., and wider literature shows a striking diversity of opinion. Thus Herskovitz (1943) is unwilling to treat with E.C.T. patients over 60 or those with any kind of heart disease (past or present) or tuberculosis. Cook (1944) considers tuberculosis an absolute contraindication. On the other hand, Feldman *et al.* (1946) have given E.C.T. to patients over 80, and Kalinowsky and Hoch (1946) do not think it contraindicated when the systolic blood pressure exceeds 200 mm. Hg or in the presence of active tuberculosis. In the main, however, its use in impaired cardiac function, chest disease, old age, and frailty is regarded as requiring careful consideration and as involving considerable risk (Sargant and Slater, 1944). Fractures, except slight vertebral crush fractures, are generally regarded as an absolute contraindication to E.C.T. A number of deaths have been reported where unmodified E.C.T. has been given to patients with heart disease (Jetter, 1944; Napier, 1944) and to elderly patients (Evans, 1943; Mayer-Gross, 1945), and sometimes treatment has had to be discontinued (Jones, 1943). Will and Duval (1947) report a death due to reactivation of old tuberculosis following E.C.T., and mention several other cases in which inactive tuberculosis became active and spread rapidly after treatment. Twenty-nine deaths due to unmodified E.C.T. have been collected by Will, Rehfeldt, and Neumann (1948). This bears out the general conclusion that in such patients unmodified E.C.T. is not without danger.

Respiratory paralysis, which accounts for most of the deaths so far resulting from curare-modified E.C.T., apparently presents no danger if the technique described by Hobson and Prescott (1947), and employed by us, is used. The electrocardiographic evidence that curare should not be used in cases of heart disease (Jones and Pleasants, 1943) is not borne out by clinical experience or by physiological experiment (McIntyre, 1947). Kalinowsky and Hoch (1946) state that patients dislike the sensation of curarization, but we have found that many patients prefer the modified treatment here described to ordinary E.C.T., as the anaesthetic eliminates the unpleasant feelings associated with E.C.T. as well as those associated with curare.

Technique

Our technique is the same as that employed by Hobson and Prescott (1947), except that a greater quantity of curare is used in order to modify the convulsion more effectively. In this way not only is the risk of fracture abolished but