unsteadiness when she walked. On examination she was pale but fairly well nourished; her tongue was smooth, the lower abdomen was distended, and there was oedema of the ankles. The blood pressure was 100/60 and there were signs of a sensory peripheral neuritis.

A four-day fat balance showed 78% absorption; the haemoglobin was 8.2 g. per 100 ml.; M.C.V., 133 cubic microns; M.C.H.C., 33%. The bone marrow was partly normoblastic and partly megaloblastic. A fractional test meal showed a histamine-fast achlorhydria, and a glucose-tolerance test was normal. A barium-meal examination showed distension of the small bowel with delay in transit. An injection of 1,000 µg. of vitamin B₁₂ raised the haemoglobin to 10.9 g. per 100 ml. She was then given chlortetracycline, 250 mg. four-hourly for ten days; the diarrhoea diminished, and the reticulocyte count rose from 1% to 12% by the eighth day of treatment. She resembled the cases described by Naish and Capper (1953) in whom the anaemia and steatorrhoea were secondary to a stagnant loop of small intestine. At laparotomy there was a greatly dilated blind loop of gut 3 ft. (90 cm.) from the ileocaecal valve, and a resection was done. She made a complete symptomatic and haematological recovery.

Steatorrhoea Secondary to Multiple Jejunal Diverticula

Case 37.—A woman aged 79 presented with weight loss, anorexia, and a history of intermittent attacks of diarrhoea for several years. The stools were formed, pale, and bulky. Ten years previously a macrocytic anaemia had been diagnosed at another hospital and she had had regular injections of liver ever since.

On examination her general condition was good and her blood pressure was 170/95. A barium-meal examination showed multiple large jejunal diverticula. A single 24-hour stool contained 20.7 g. of fat; the haemoglobin was 14 g. per 100 ml.; M.C.V., 112 cubic microns; M.C.H.C., 31%. It seems likely that the steatorrhoea, macrocytic anaemia, and jejunal diverticula are associated. A similar case has recently been reported by Dick (1955). He suggests that stagnation and infection of the diverticula may play some part in the causation of the steatorrhoea and anaemia.

Discussion

The differential diagnosis of the cause of steatorrhoea is of primary importance so far as the treatment of the condition is concerned, for in certain cases of secondary steatorrhoea surgical treatment may be curative. In cases of secondary steatorrhoea with some clinically obvious mechanism of disease process, as in chronic obstructive jaundice, the treatment is that of the primary disease and not of the steatorrhoea, which is merely a symptom; moreover, the differential diagnosis of such conditions from idiopathic steatorrhoea is not difficult.

However, those cases of secondary steatorrhoea with a clinical picture similar to that of idiopathic steatorrhoea, such as the post-operative blind-loop syndrome or pancreatitis, must clearly be differentiated from this condition. The main points of differential diagnosis have already been considered, but certain diagnostically helpful points will be mentioned briefly again. Idiopathic steatorrhoea often presents a definite clinical picture, the correct diagnosis being suggested on these grounds alone. Thus steatorrhoea in a patient who is otherwise fit and well nourished is more suggestive of chronic pancreatitis than of idiopathic steatorrhoea, as in Case 15. Previous history of abdominal operations (Case 36), a history of childhood diarrhoea (Case 11), the presence of a small-bowel lesion on barium-meal examination (Case 37), and tests of pancreatic function (Case 15) may also be useful.

Finally, if there is still some doubt about the aetiology, together with a reasonable chance of a correct diagnosis leading to successful treatment, a laparotomy should be considered: Case 29 partially fits into this category, but a correct diagnosis would only have enabled palliative therapy to be carried out.

Summary

Forty cases of steatorrhoea are reviewed. Of these, 13 were primary steatorrhoea, 23 secondary, and in 4 cases it was not possible to be certain of the type.

The diagnosis of steatorrhoea is discussed, and the importance of excluding an underlying aetiological lesion is emphasized.

Our thanks are due to Dr. F. Avery Jones, under whose care most of the patients were, for his encouragement and advice. Permission to publish cases under their care was kindly given by Drs. R. A. J. Asher, K. P. Ball, and T. D. Kellock.

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FUNCTIONAL UTERINE BLEEDING*

BY

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Three years ago I was lucky enough to be enabled to visit Canada and the U.S.A. through a grant from my hospital, and it was whilst working in the Royal Victoria Hospital, Montreal, under the aegis of Dr. Newel Philpot that I began to appreciate the importance of the Papanicolaou smear in the routine examination of patients attending the out-patients department and the well women's clinic.

I decided to try, by the use of this technique in my own clinics, to get some rational basis for treatment in cases of uterine bleeding which could not be explained on routine clinical findings, and, further, to check the results of therapy by a series of such smears. I believe I am right in saying that, at the outset, vaginal smears were used to gain some information about ovarian function from the assessment of the cornification, etc., and that cancer detection was a later development.

Through a research fellowship established shortly after my return home, and through the work of my colleague Dr. Mary Egerton, the holder of this fellowship, it has been possible to examine and follow-up a number of patients during the past two and a half years, and it is largely because of this work that I would discuss some aspects of the problem.

Definition

By functional uterine haemorrhage I understand bleeding from the uterus for which no cause can be found in the general condition of the patient, on clinical examination of the pelvic organs, or on curettage of the cavity. This last proviso requires some amplification. I am confident that, in general, a diagnosis of functional bleeding should not be

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accepted without curettage to exclude such conditions as retained products of conception, placental polypi, and, of course, neoplasms—a small subendometrial fibroid or a carcinoma of the body of the uterus or endocervix. An exception to this proviso might be entertained in the case of an adolescent, provided always that response to treatment was speedy and satisfactory. Otherwise, these patients, too, should be examined under anaesthesia and curetted to confirm the diagnosis fully.

Forms Which Functional Uterine Bleeding May Take

The term "functional uterine bleeding" implies, to my mind, an alteration in the usual cycle of any given patient. Cases where the interval is twenty-one days, cases where the interval is five or six weeks, are known to us all and appear to be normal in the individual; the duration of the flow also varies with the individual, and menstrual periods of two days or seven days would be normal in certain women.

It is with the patients who have a deviation from their own accepted normal that we are here concerned. It is recognized that some girls at puberty do not settle down for a few months to a rhythm which could fall within average limits, but if they do not so settle, or if the flow is so profuse or prolonged as to affect their general condition, then these patients too would fall into the big group under consideration. When these points have been considered and allowed for, functional bleeding may present as: (a) menorrhagia—prolonged and/or profuse menstrual periods; (b) frequent periods—that is, a definite reduction in the length of the cycle; or (c) irregular cycles—sometimes long, sometimes short.

Irregular intermenstrual bleeding is not included, as, with the exception of ovulation bleeding, this symptom usually indicates an abnormality of the pregnant state, or a new growth of the reproductive tract. Also, in my view, post-menopausal bleeding should never be included, though the production of vaginal bleeding in post-menopausal women as a result of the administration of oestrogens, for varied and at times invalid reasons, confuses the issue to a considerable extent and must have led to the performance of a large number of operations for curettage otherwise uncalled for.

The great majority of patients under review sought advice for prolonged and/or profuse menstrual periods, but, in some, irregular periods and shortened cycles were the prominent symptoms.

Procedure

When a patient seeks advice for some symptom falling within the group under consideration, her age and marital status are noted and a careful history is taken with regard to the present symptom or illness; her previous health; her obstetric experience, including pregnancies which have been interrupted by miscarriage, ectopic implantation, or mole formation; the family history; and menstruation.

The blood pressure is recorded, the urine examined, and the haemoglobin estimated. The patient then has a general physical examination, with due regard to the particular importance of diseases associated with hypertension, diseases of the blood, anaemias, and diseases of the endocrine glands—for example, the thyroid. I think, too, that an attempt should be made to assess her nutritional state and her psychological condition. In my experience, menorrhagia is often allied to unsatisfactory contraceptive methods (coitus interruptus) or to disturbed sexual or marital relationships.

Moving now to the more strictly gynaecological field, the abdomen is investigated, the Papanicolaou smear is taken, and the pelvic organs are examined digitally and by speculum. In the present series the Papanicolaou smears have all been taken by a gynaecologist, under direct vision from the posterior fornix and cervix in married and parous women, and by aspiration from the posterior fornix in virgins and children. The smear from the cervix is used for cancer screening and that from the posterior fornix for

endocrine estimation. It has not always been possible to take the smear at the most appropriate or advantageous point of the cycle, since the procedure is a routine one in my clinic at the first visit; but, where necessary, the patient has been given an appointment at the correct date and the smears have been repeated. It has occasionally been found necessary to repeat the smear when an overlying discharge due to vaginitis, possibly from a trichomonal infection, or a cervicitis, has obscured the picture.

If on clinical examination no general or local cause has been found to account for the presenting symptom of uterine bleeding, the patient is curetted, the operation being performed in the second half of the cycle. Owing to the severe pressure on hospital accommodation, this procedure has been omitted in a few cases of adolescents and a few adults whose main complaint is an irregular cycle, but curettage and histological examination of the endometrium should be regarded as an integral part of the diagnosis.

By the study of the Papanicolaou smears Dr. Egerton and I have divided our cases of functional bleeding into four groups:

1. *Menorrhagias of Puberty*.—Here the smear shows low hormonal levels but an oestrogen preponderance at low level. There is evidence that the cycle is anovulatory and the endometrium has undergone no distinct pathological changes.

2. *Menorrhagias of Early Reproductive Life*.—These patients are usually between the ages of 20 and 30 years. The hormonal levels are low generally, with no undue preponderance of either hormone. The cycle is ovulatory and the endometrium within normal limits.

3. *Late Reproductive Life (Ages 35–45 Years)*.—Here the endometrium deviates from the normal. It may show an exaggerated proliferative phase, or there may be a hyperplastic polypoidal endometrium characterized by distension of the tubular serous-secreting glands and often by small areas of superficial necrosis. But the histological findings on curettage do not give a complete picture, and the smear shows that these cases should be subdivided into (a) those with an oestrogen preponderance but evidence of some progesterone effect, with the total hormones at a reduced level; and (b) those with a high and persistent oestrogen level. In the first subgroup the patients have an exaggerated proliferative phase in the endometrium, with some secretory effect towards the end of the cycle. In the second subgroup are those cases with a polypoidal endometrium, and in these patients it may be possible to detect follicular retention cysts of the ovary on clinical examination.

4. *Menorrhagias of the Menopause*.—The curettage is typically scanty to the naked eye, but histologically within normal limits. The cycles are anovulatory, and the smear indicates a reduction in hormonal levels but with oestrogen preponderance.

It is of some importance to emphasize that these groups are not necessarily as clear-cut as this arrangement might suggest: there is inevitably some overlapping, but the classification has proved useful in determining treatment, particularly where radical measures are contraindicated.

Treatment

There are, I think, four possible lines of treatment that should be reviewed.

Firstly, simple symptomatic treatment may be considered, and probably will be tried at the onset before a full diagnosis has been made. This treatment would consist of correction of any secondary anaemia and administration of drugs to control the actual flow by acting on the uterine muscle. I am convinced of the importance of dealing with the anaemia, and for this purpose use iron and some form of proteolysed liver together with vitamin B. If, as I believe, the bleeding is due to endocrine disorder, the oxytocic drugs are unlikely to be effectual, and this indeed in practice proves to be the case.

Secondly, there are operative measures. Curettage, apart from its diagnostic importance, is valueless in the first, second, and fourth groups, where the endometrium does not show definite hypertrophic changes. It is, however, of some value in the metropathia group, though usually the improvement is transitory. It is a little difficult to see why

this should be so; but tentatively I suggest that after a thorough curettage the endometrium may not build up to the fully developed polypoidal or hyperplastic state characteristic of this group for several cycles. Even more tentatively I put forward the idea that curettage may stimulate normal ovarian function temporarily and so produce, at least in the younger patients, some progesterone effect in subsequent cycles. Curettage therefore has a place in the management of metropathia in the woman nearly approaching the menopause, when the transitory improvement may tide her over the intervening interval before cessation of the periods. The operation of castration by removal of the ovaries I do not consider. It is obviously contraindicated in adolescents and women under 40, and in the woman over 40 removal of the ovaries and retention of a pathological uterus does not make sense. Personally, I would not accept removal of one out of two comparable ovaries: I can see no logic in this, since experience shows that a patient with one ovary is indistinguishable from a patient with two in respect of her ovarian hormone production. There remains hysterectomy. This should be very seriously considered in women over 45, or even over 40. A dysfunctioning and potentially dangerous organ is removed and the condition is cured. The strongest argument against such treatment is that based on psychological grounds. I submit that such grounds will, in some patients, provide a weighty and valid contraindication to hysterectomy. In my view, when hysterectomy is being carried out for this condition in a woman over 45 the ovaries should be removed. I have not observed more severe menopausal symptoms after this procedure at this age than when the ovaries are left. In women under 45, and provided the ovaries are normal to direct clinical inspection and examination, each case should be dealt with on its merits, but I favour leaving the ovaries as a general rule. In younger patients hysterectomy may be the only means of relieving them of their symptoms and ill-health, but must be regarded as an expression of failure in both diagnosis and treatment.

Thirdly, radiotherapeutic measures demand consideration. In women of 40 or over who are unsuitable for major surgery on account of some coincidental condition such as bronchiectasis, cardiac insufficiency, etc., the use of x rays to destroy ovarian activity can be good and satisfactory treatment. On the whole, I prefer this form of radiotherapy to the insertion of radium into the uterine cavity. I have formed this opinion from my experience that intrauterine radium is less certain in its action, which I believe to be essentially destruction of the endometrium, and, moreover, that it may have the distressing sequel of a troublesome and persistent vaginal discharge from the necrosed endometrium. In the younger patient radiotherapy has only the most limited place, if any. Again I could say it is a confession of failure, but it might be used as intrauterine radium in an attempt to produce an effect limited in time and with conservation of the uterus. I have one such case in mind among my own patients, dating back to my early days of practice when hormone treatment was rudimentary. This girl resisted all efforts to control her menorrhagia by drugs: she had intracavity radium, leading to amenorrhoea for some years, but subsequently menstruation returned and she bore a child.

Finally, there is treatment by hormones, and it is here that we have found the Papanicolaou smear of enormous value both in directing and in controlling treatment. I think it is fair to say that often endocrine treatment in functional bleeding has been largely a matter of "by guess and by God," and yet it is a potentially important method of dealing with such cases, especially in adolescents and the younger women in whom radical surgery and radiotherapeutic measures are contraindicated. The work we have been doing is an attempt to get a sound basis for this line of therapy, and also to check the results by the effects reflected in the smears. With this end in view, Dr. Egerton has examined 879 patients and some 2,900 smears. These were by no means all cases of functional bleeding, but an

effort was made to assess the smears with regard to the value of the picture that they gave of the ovarian function. We now have records of 47 patients whose functional bleeding was treated, and whose treatment was controlled on the evidence provided by vaginal smears. In the menorrhagias of puberty and of the menopause we have found usually low hormonal levels but with relatively high oestrogen production at these low levels. In the early reproductive life there is generally a low hormone level, though not an unbalanced one; and in the later reproductive life an unbalanced hormone production with marked excess of oestrogens. In this way we have had a pointer in selecting the most appropriate hormone to use: sometimes oestrogen, sometimes progesterone, and sometimes both hormones given in cyclical fashion.

This is not the place to discuss in detail the various types of cell found in the smears and on which the diagnosis is based, but the study has been based on the description given by Papanicolaou, Shorr, Bonime, de Allende, and others; and the cornified, precornified, and deep-layer cells described by these workers have been counted and their arrangement has been observed.

Illustrative Cases

When treatment is being undertaken a planned series of smears is used to check the results of therapy cytologically and to compare these results with the effect of the drugs on the symptoms. A brief reference to three cases may help to elucidate the problem.

Case 1.—This patient, aged 14, began to menstruate in April, 1954. The flow was heavy, lasting some seven days, and the intervals were long at first. In August she was referred to hospital because of prolonged menstrual loss, 14–20 days. The endometrium showed no pathological change, but in the smears there was evidence of oestrogen preponderance at low level. Before being referred to hospital this girl was treated by progesterone without effect on the symptoms, but an improvement is being achieved by giving both hormones in cyclical fashion. Our hope is that we shall tide the patient over an interval during which the ovaries will begin to function normally.

Case 2.—A married woman aged 34 came with the complaint of increasing menstrual loss from four days up to twelve or fourteen at regular intervals. She was found to have a generally low hormonal level and was treated with both hormones, given cyclically. In her case the repeat smears were valuable in deciding the amounts to be given. Her cycle became regular and she lapsed in her attendance. After an interval of ten months the symptoms recurred and she returned to hospital. The low hormonal level was again found, and she is again responding to treatment.

Case 3.—A married woman aged 39 came to hospital saying she wished to have a hysterectomy. She gave a history of long heavy periods (14–20 days) at intervals of five to six weeks for five years. Her previous cycle had been 3–4/25–26. She had been given various "pills" and "injections" and had twice been curetted. The endometrium here showed persistent proliferation and the smear an intense oestrogen preponderance with no evidence of progesterone effect. On progesterone therapy the loss has been reduced to normal, but the intervals remain long. In her case I anticipate that treatment is in the nature of replacement therapy and will have to be continued over a prolonged period.

Conclusion

I submit that in cases of functional bleeding the vaginal smear is an important adjunct in diagnosis and a valuable aid in planning and controlling treatment, though it in no way supersedes clinical examination and diagnostic curettage; nor does it exclude surgical treatment, but it does help to place hormone therapy, where indicated, on a rational and controlled basis and so avoids radical surgery in the younger woman with this disabling complaint.

Summary

Functional uterine bleeding is defined as bleeding from the cavity of the uterus for which no cause can be found by general or local clinical examination, or by curettage of the cavity. Post-menopausal bleeding is considered to be of a different character. The diagnosis is made after full physical examination, both general and local, with study of the vaginal smears by the Papanicolaou method, and confirmed by curettage and microscopy of the endometrium. The cases are initially divided into age groups.

Treatment is considered under four headings—symptomatic, surgical, radiotherapeutic, and hormonal—and the indications briefly discussed. The importance of conservative measures in adolescents and in women under the age of 40 is emphasized.

It is claimed that the vaginal smear is a valuable method of assessing ovarian function and of diagnosing variations from the normal, thereby providing a rational basis for hormonal therapy. Such therapy should be controlled by a planned series of smears.

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CONTRIBUTIONS OF NEURO-ANATOMY AND NEUROPATHOLOGY TO PSYCHIATRY*

BY

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It is sometimes forgotten, amidst the luxuriance of the psycho-analytic jungle, that the roots of our knowledge lie embedded in the soil of the basic sciences. This soil is often alleged to be an extremely inhospitable medium for the growing plant of psychiatry to flourish in, and there has been, particularly in the American continent, such a shift away from these basic sciences as to be quite alarming. It is my contention, and it will be my aim, to show that neuro-anatomy and neuropathology have contributed at least as much as any of the other basic sciences to our present understanding of mental disorder. For such a vast field a review such as this can either be all-embracing and panoramic or, on the other hand, can select certain topics for critical consideration. It is this latter method I have chosen, the topics being schizophrenia, the anatomical problems of leucotomy, the epilepsies, and the senile and presenile dementias.

Before we consider these groups in general, it is proper to consider the techniques which are now available for their investigation. Unfortunately the revolutionary developments in physical science have not, as yet, had their fullest application to anatomy and pathology. The basic methods of microscopical work remain very much unchanged. Sections are stained by a variety of new stains, it is true, but the microscope remains the

chief tool. Both anatomy and pathology have, however, become more functional, in the sense that descriptive studies are more and more closely integrated with studies of function. The direction which these two sciences are taking is toward a greater understanding of function in its relation to structure, and as a result there is a considerable use of techniques derived from other fields. Physiological neuronography, for instance, has added a great deal to our knowledge of brain anatomy, whilst histochemistry is developing our understanding of cell structure in terms of biochemistry. It seems proper, therefore, to outline briefly some of these new techniques before passing on to consider the results of their application.

New Techniques

Of the more orthodox methods, the use of specialized silver impregnation methods has been most rewarding. The advantage of these stains is that the actual axis cylinders, and particularly their terminal arborizations, can be determined, irrespective of the degree of myelination. M. Meyer (1949), for instance, was able to trace a direct pathway from the dorsal frontal convexity (approximately areas 8 and 6 of Brodmann) to the mammillary bodies and other parts of the posterior hypothalamus. The development of histochemistry will soon have important repercussions in these two sciences. Lison (1936), in France, may be regarded as the first to organize knowledge in this field, and since then there have been rapid advances. A known chemical reaction is used in order to identify substances within a histological preparation, but certain physical properties of substances are also made use of, such as fluorescence, ultra-violet or x-ray spectrography, and tracer techniques. The chemical substances in the tissue must first be immobilized in the situations where they occur during life, and the freeze-drying technique has therefore been extensively used. In addition, the chemical reaction or physical method used in order to identify the substances within the section must not interfere with tissue structure, and must produce a reasonably stable result and, preferably, a highly insoluble and deeply coloured precipitate.

In the nervous system enzymatic activity in relation to normal and diseased tissue is clearly an important field for work. Naidoo and Pratt (1954) have traced the development of adenosine 5'-phosphatase activity in the rat cerebral cortex during maturation, and have shown that there is an increase in enzyme activity which is greatest between 15 and 80 days of life. This activity appears to arise in nerve fibres, and may be related to myelination. They have also (Naidoo and Pratt, 1955) shown that in chickens deficient in vitamin B₁ there is a significant increase in the thiamine pyrophosphatase and alkaline phosphatase activity in the optic tectum, but no change in the acid phosphatase activity. The effects of physical treatments such as leptazol can be investigated experimentally, and the method is full of promise both for neuro-anatomy and for neuropathology.

At the other end there have been advances in microscopy which are perhaps not as well known as they should be. The phase contrast, the reflecting microscope, and the electron microscope have all their individual advantages over orthodox microscopy. To date, however, technical difficulties in dealing with biological specimens have hindered progress, and, to the best of my knowledge, the contributions to our specialty have been negligible.

Schizophrenia

Of the topics which I have chosen for special consideration, that of schizophrenia presents the most difficult problems. In spite of this, anatomical and pathological research into schizophrenia has indirectly opened up new vistas in our understanding of neuro-anatomy. The study of post-leucotomy brains at the Maudsley Hospital by Professor Meyer and his associates has added an impressive chapter

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