attention to the positive group alone, you can never be certain that the screening process is sensitive enough for your needs—that is, you can never find out whether the test fails to detect early cases.

"Ex Post Facto" Experiments

A great deal of information relevant to problems in medicine has been collected in the form of routine records by agencies such as public health departments. Sometimes these data have been gathered without any special research project in mind, but when they are reconsidered they seem to be pertinent to some problem. These data then constitute what sociologists refer to as an *ex post facto* experiment.

Information obtained in this way is often illuminating, but there are certain limitations to its use, and these are chiefly concerned with the problem of biased sampling. Is it possible to define a universe of which the cases under consideration can be regarded as a sample, and has the sampling been random? If these questions cannot be answered satisfactorily then the standard methods cannot safely be used to test hypotheses concerning the data, and any conclusions drawn may lack objectivity.

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ADRENAL PSEUDOHERMAPHRODITISM

BY

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Adrenal pseudohermaphroditism, or pre-pubertal virilism, is a syndrome characterized by the masculinization of the female. It is associated with simple enlargement and pigmentation of the adrenal cortex, and the excretion of large amounts of 17-ketosteroid in the urine. The condition is clearly differentiated from true hermaphroditism and the intersexes in two respects. Whereas in both the latter there is a persistence of Wolffian derivatives and no rise in 17-ketosteroid excretion, the reverse is true of adrenal pseudohermaphroditism.

In relation to the aetiology of the disease it is of interest to note that Professor Barr, of London University, Ontario, has examined portions of the skin taken from some of our patients and found in every case the nuclei were of female morphology (personal communications). The available evidence does not advance us beyond the vague generalization that the condition is due to secondary hormonal influences acting upon a genetically determined female embryo during the early stages of foetal development. The critical period of any hormonal action would seem to be between the 11th and 21st weeks—that is, between the time of disappearance of the Wolffian derivatives and

the completion of Müllerian development. Whether the stimulus derives from the mother or arises from some factor inherent in the foetal endocrine system are questions which have yet to be determined. Whatever theory is advanced, it must take into account the strong familial element associated with the condition, the evidence for which is cited later.

Our work on this problem of the masculinization of the female began in 1926; since then we have collected 37 cases belonging to the group of congenital pseudohermaphroditism, and the present communication is based on clinical and biochemical data compiled on this series. Previous communications have dealt with a number of the early cases (Broster and Vines, 1933; Broster *et al.*, 1938), but within the past two years many of these, together with more recent patients, have been subjected to a closer and more critical study made possible through the collaboration of Dr. J. Swale, Professor J. Patterson, and Dr. B. Camber.

General Features

Symptoms.—The general features depend on the age of the patient and the severity of the lesion. In infancy the earliest sign is an enlarged clitoris with a persistent urogenital sinus. Later there may be precocious puberty as indicated by premature growth of pubic followed by axillary hair and raised ketosteroid output. As the patients grow up the somatic development is in advance of the chronological age and the short stature is characteristic. If, however, the patient is not seen until the age of normal puberty the diagnosis is made clear when the secondary sex characters of the female do not appear and facial and somatic hair of the male type grows and the voice becomes deep. More recently it has become known that patients suffering from congenital hyperplasia may die in early infancy or childhood from adrenal failure, and in six instances a history was obtained of episodes suggestive of Addisonian crises.

Hirsuties.—Except in infants, and one adolescent, hirsuties of male distribution has been a prominent feature in all our cases. In two of the older women temporal recession and apical baldness were present.

Breasts.—The great majority of our patients have shown no breast development at puberty. In only eight were they rudimentary, and some of these had received oestrogen therapy.

Sex Development.—On examination the clitoris is found to be enlarged and curved downwards. From the area of the fraenum two small folds of skin gradually diverge to encircle a small orifice which is the persistent urogenital sinus. No urethral orifice is visible externally. The cervix and uterus are small and generally not palpable. In only one patient was there a small urethrovaginal fistula. At laparotomy the ovaries have been in their normal position and have not shown any marked macroscopic changes. Some appear normal, while others are fibrotic and cystic. Histologically they show oogenesis and atretic follicles as well as cysts. Three patients about the age of 6 showed numerous ova, atretic follicles, and numbers of cysts typical of isosexual precocity. One of these (M. Ba.), who had normal follicles with some abnormally mature ova, showed a sexuality much in advance of her age. As is reported later, this sexual precocity was related to signs of undue maturity recorded by the electroencephalogram. A few reports recorded luteum cysts, and in one case there was no abnormality apart from suspended activity. Primary amenorrhoea is almost invariably present, although two patients had a slight show after puberty.

Clinical

History.—Significant features in the family histories of 50% (18) of the patients in this series were familial endocrinopathy, maternal disorder during pregnancy, mixed racial origins, or the presence in the individual of associated congenital abnormalities. With adrenal disease in general we have been struck by the frequency with which it occurs

in the offspring of mixed racial marriages, more especially of the Nordic and Mediterranean strains. In this series four families showed affected siblings. Two families were of special interest in that, as well as the affected sister, there was a brother suffering from isosexual precocity due to adrenal cortical hyperplasia. In another family there were two sisters suffering from adrenal pseudohermaphroditism, a brother and sister with congenital dislocation of the hip, and one normal sister. The mother of the fourth family suffered from toxæmia of pregnancy while carrying two pseudohermaphrodite sisters, but not with the other siblings. Endocrine disease, such as diabetes and thyrotoxicosis, was present in four families, and familial hirsuties in another three families. In five instances there was evidence of the "big baby syndrome." The concomitant congenital deformities included "webbed toes," Madelung's deformity, and deformity of the carpus.

Sexuality.—Our opinion, arrived at independently of Professor Barr's evidence, that these patients are essentially and fundamentally feminine receives further support from Dr. Randell, who has conducted a psychological investigation into some of these patients and reports: "The fact that these

Adrenalectomy

Before discussing the operative results in detail, two general observations with regard to adrenalectomy may be recorded. The first point is that, in our experience, the high renal approach via the last rib is the most satisfactory. Secondly, the operation has entered upon a safer phase since the advent of cortisone. The changed situation with regard to adrenalectomy is analogous to that undergone by subtotal thyroidectomy as a result of the introduction of anti-thyroxine compounds. Indeed, the analogy may be pushed further from the technical point of view in that an adrenal is more oedematous, adherent, and difficult to remove after cortisone, as is the thyroid after thiouracil.

Unilateral adrenalectomy (following an exploratory laparotomy) for adrenal pseudohermaphroditism was started in 1926 (Broster *et al.*, 1932) and our early experience was confined to adults. The results were encouraging enough to warrant further trial, and still better results were obtained when we began to operate before puberty. More recently we have carried out subtotal adrenalectomy. In that the results of this treatment are more favourable, we now consider it to be the operation of choice in advanced cases. Out

TABLE I

Patient	Born	Adrenalectomy	Periods	Breasts	Voice	Notes
C. Ha.	1939	Unilateral, 21/11/44	Regular since 1952	Normal development	Female	Mild case
M. Am.	1938	Subtotal, 11/12/44 and 20/2/48	23/5/53, irregular	Normal for age	Deep	Marked case
K. He.	1938	Subtotal, 21/2/47 and 10/1/48	Periods irregular, 25/2/53	Normal development	Broken; not female	Brought up as a boy. Marked case. Cortisone 17/8/53
I. Ma.	1937	Unilateral, 1949	One period, July, 1953	Breasts forming	Higher in tone; pitch feminine	Marked case. Cortisone 6/5/53
H. Ba.	1939	Unilateral, 14/5/48	None	Retarded	No change	Given cortisone 1/5/53
B. St.	1941	Unilateral, 24/7/53	One period with cortisone	Well formed	Voice improved	Operation after one year's treatment with cortisone

girls suffering from virilism do not show any marked feminine traits accords with the social and psychical concomitants of being 'hairy.' On the other hand, I do not consider that they have marked masculine traits. In every case except one the psyche was orientated in a feminine direction. In adolescent girls this can be said with less assurance as they were immature, but it is certainly true of adults. The level of psychic drive is perhaps generally higher than the average for a woman. The one case excepted, brought up as a boy, still retains masculine traits to some degree. This, however, could be accounted for by the nature of her upbringing." We therefore advise contrary to the expressed views of Wilkins (1950) that irrespective of their background these patients should be brought up as females. To this end we advise removal of the clitoris so as to restore the external genitals to the normal female configuration.

Encephalography.—An inquiry into the encephalographic records of these patients has been started by Dr. Frank Elliott, who summarizes his preliminary findings as follows: "Of the five cases tested, four had abnormal records. Two (H. Ba. and M. Am.) showed a degree of maturity quite unusual in children of this age; there were no slow waves, alpha rhythm was well marked, and there was considerable beta activity. These findings are the reverse of what occurs in suprarenal deficiency. C. Ha., on the other hand, exhibited gross bilateral theta activity and some normal theta on over-breathing. These changes were present before cortisone therapy, and are probably due to a lesion in the hypothalamus. Finally, I. Ma., brought up as a boy, had a slightly abnormal record with multiple rhythms in the parietal area. The significance of this observation is not yet clear.

Somatotypes.—Most of the patients have been somatyped by Mr. Wilson, of the photographic department of the Royal Society of Medicine, in order that the details of development and configuration might be studied objectively. The photographs provide not only a permanent record, but also furnish the means of studying the natural history of the disease and the effects of treatment. They clearly demonstrate a characteristic physical type—height generally less than 5 ft. (152 cm.), short muscular body, shoulders broad relative to the hips, legs short relative to the body, deep chest, and tendency to lumbar lordosis with steatopygia.

of 37 cases operated on there have been 6 deaths, all of which occurred before cortisone was available. Apart from crises during the immediate post-operative period, only one of our patients has shown evidence of late Addisonian crisis. This exceptional case was treated with cortisone for one year before unilateral adrenalectomy.

Hirsuties when due to adenoma or carcinoma (except with secondary deposits) is shed rapidly after operation and does not recur, but in adrenal pseudohermaphroditism the results are less satisfactory unless bilateral subtotal adrenalectomy is carried out before puberty. The hair on the head does not grow beyond the shoulders, but does so more luxuriantly after operation and to a less extent after cortisone.

It was only when we came to deal with patients who had not yet reached puberty that clinical improvement of an entirely different order was achieved. Six of these cases have now had operative treatment, and since they were of different degrees of severity they received varying forms of treatment—unilateral in one case, subtotal in two cases, unilateral and cortisone in three others. The results of treatment are summarized in Table I.

The secondary sex characters showed a degree of development which was absent in our adult patients. By the application of one of these three methods, the choice being governed largely by the severity of the condition, these young girls may, even if somewhat retarded, now expect to develop their secondary sex characters.

Results

In adrenal pseudohermaphroditism the 17-ketosteroid excretion is essential to diagnosis. The values are always very much raised. In Table II our results are recorded in com-

TABLE II

Age Range	Normal Range of 17-Ketosteroid Output (mg./day)	Adrenal Cases; Range of 17-Ketosteroid Output (mg./day)
2-5 years ..	*0.29-1.20	9.8 (1 case)
6-8 " ..	*0.26-1.55	6.5-44.0
9-12 " ..	*0.23-2.30	21.0-56.0
Adult (female) ..	†3.0-16.0	38.0-130.0

* Values recorded by Wood and Gray (1949). † Values from our own records.

parison with the normals of the corresponding age group. They show, when taken in conjunction with the more comprehensive data for pre-pubertal virilism compiled from the literature by Mason and Engstrom (1950), that the natural history of the disease is associated with steadily mounting 17-ketosteroid excretion, the rise being prolonged well into the third decade. This feature has not always received sufficient recognition, especially by those who have argued that because a post-operative rise in 17-ketosteroid output

FIG. 1.—Effect of unilateral adrenalectomy in a patient (F. Mu.) aged 35-38.

FIG. 2.—Effect of unilateral adrenalectomy and cortisone in a patient (P. Wa.) aged 15-22.

Our experience shows that when unilateral adrenalectomy is performed on adolescents and adults there is some degree of clinical improvement in nearly all cases. The patients look less coarse and more refined, the subcutaneous fat is softer and more evenly distributed, the texture of the skin and the complexion are improved, acne lessens, the hair of the head grows longer and loses its greasy appearance, while that on the body becomes more amenable to depilation. In these cases, however, there is no very obvious correlation between the degree of clinical improvement and the extent of the depression of the 17-ketosteroids after operation.

Dehydroepiandrosterone (D.H.A.) Excretion

Of the 17-ketosteroids excreted in the urine, D.H.A. is of special interest because it is believed to be derived solely from the adrenal cortex. When it was found in virilizing

adrenal tumours that D.H.A. amounted to over 50% of total 17-ketosteroids it became important to find a ready, direct test showing its preponderance in the urine. A test fulfilling this purpose was devised by Patterson (1947). It is based on the finding that when D.H.A. is subjected to the action of sulphuric acid under certain conditions a blue colour results. As only virilizing tumours yield enough D.H.A. in the urine to give a positive result under the prescribed technique, the test could be used for diagnosing the presence of this lesion. The work has now been extended so as to provide a quantitative method for measuring D.H.A. excretion in patients suffering from adrenal pseudohermaphroditism (Patterson and Swale, 1953).

The application of this method to the present series shows that, biochemically, the patients fall into two distinct groups. The first (type α) is characterized by a relative absence of D.H.A., whereas the second (type β) shows appreciable amounts of D.H.A., the most important of the beta 17-ketosteroids. Of the 19 investigated, 6 were of type α (excreting less than 0.5 mg. of D.H.A. a day) and 13 were of type β (excreting 1-25 mg. a day). The detailed results for type β cases are recorded in Table III.

In relation to these findings it may be pointed out that Scowen and Harris (1951) failed to find D.H.A. in appreciable quantity in the urine in a study of nine cases of adrenal pseudohermaphroditism, whereas Dingemans *et al.* (1946), provided evidence for the presence of large amounts in their series. These apparently conflicting results are reconciled by the demonstration here of the existence of two types within the same clinical group.

The possible clinical significance of the two different biochemical types is now under investigation. The amount of D.H.A. excretion does not appear to bear any obvious relation to the clinical picture, and in the light of our present observations it cannot be said that D.H.A. excretion is a

FIG. 3.—Effect of subtotal adrenalectomy in a patient (P. Go.) aged 22-27.

TABLE III.—D.H.A. Excretion in Cases of Type β

Patient	Age	Total 17-K.S. (mg./day)	D.H.A. (mg./day)	D.H.A. as percentage of Total 17-K.S.	Remarks
C. St.	31	88.0	18.0	20.0	Pre-operative
J. Cl.	17	78.0	5.4	7.0	"
B. St.	12	52.6	6.8	13.0	"
A. He.	22	69.0	19.0	27.5	"
J. Ki.	32	74.0	6.4	8.7	Unilateral adrenalectomy, 1936
A. Go.	32	45.0	9.1	20.2	Unilateral adrenalectomy, 1937
R. Mo.	18	80.0	25.1	31.3	Unilateral adrenalectomy, 1946
J. Pa.	17	84.0	6.2	7.5	Unilateral adrenalectomy, 1946
P. Wa.	22	84.0	14.9	17.7	Unilateral adrenalectomy, 1947
F. Mu.	38	38.8	2.5	6.4	Unilateral adrenalectomy, 1949
J. Du.	12	38.5	1.5	3.8	Unilateral adrenalectomy, 1950
M. Am.	14	43.0	3.4	8.0	L. adrenalectomy, 1944. R. hemi-adrenalectomy, 1948
P. Go.	27	28.5	1.1	3.9	R. adrenalectomy, 1949. L. hemi-adrenalectomy, 1949

better index of the adrenocortical function than is the total 17-ketosteroid output.

Comparison of the effect of operation and of cortisone on D.H.A. output in cases conforming to type β has not proceeded far enough to admit of definite conclusions, but preliminary work indicates that as a result of unilateral adrenalectomy D.H.A. is reduced in much the same proportion as the total 17-ketosteroids. In other words, there is no deviation from type β . The effect of treatment with cortisone compared with that of unilateral adrenalectomy depends on the dosage. When only enough cortisone has been administered to halve the total 17-ketosteroid output—that is, corresponding approximately to the reduction that can be achieved by the removal of one adrenal—there is again no deviation from type β . If, however, enough cortisone is given to bring down the total 17-ketosteroids to normal values, the D.H.A. is almost completely eliminated, signifying a change from type β to type α .

Summary

A short clinical and biochemical review of 37 cases of adrenal pseudohermaphroditism is presented.

Further biochemical studies show, on the basis of dehydroisoandrosterone excretion, that these patients fall into two distinct groups.

The effects of unilateral and bilateral adrenalectomy on 17-ketosteroid excretion are shown.

Observations of the action of cortisone on 17-ketosteroid excretion are also discussed.

Treatment is more effective when undertaken before puberty.

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PORPHYRIA

BY

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Porphyria is a disorder involving the pyrrole pigments which take part in respiratory metabolism. It is a familial condition characterized by chronic mild neurological and cutaneous symptoms with occasional acute exacerbations. I have personally attended 12 cases of acute porphyria. The first three of these patients died, the last nine recovered. They were from eleven different family groups.

In each family the genealogical tree has been worked out in the fullest detail possible. Some of the groups were large—for instance, in the first family there are 460 descendants of the first member of the family who is known to have had the typical sensitive skin. As will be seen, many in each family group have inherited porphyria. The sex distribution was about equal, but the most severe cases of acute porphyria were in women between the ages of 19 and 50. The reason for this predominance of women is discussed below. All the families seen were Afrikaners perhaps related far back in South African history. It is a common con-

dition in South Africa, and Barnes (1945, 1951) has already published the history and laboratory findings of over 40 cases. The mild cutaneous type is common in the Bantu. The condition has also been described in cattle (Fourie, 1936).

The porphyrin structure is present in haemoglobin and in certain other respiratory enzymes. When porphyrins are produced in excess they are excreted in the urine as uroporphyrins, as coproporphyrins, or as a colourless chromogen, porphobilinogen. They are also excreted in the faeces. Porphyrins may colour the urine red or reddish brown. Garrod (1923) considered that porphyria belonged to the group of familial disorders which were inherited as "inborn errors of metabolism." The disturbance in metabolism is aggravated particularly by certain drugs and by pregnancy. Porphyrinuria, usually an excess of coproporphyrins, may also occur in liver disease, anaemia, or after poisoning by certain chemicals, in individuals who do not suffer from familial porphyria.

My experience is limited to porphyria in the adult, when it presents a familial syndrome which is characteristic. Unfortunately, however, the syndrome can best be seen in retrospect, and during a remission it is often difficult to diagnose. In the acute stage diagnosis may be made too late to save the patient's life. It is a syndrome that is not well described in the medical textbooks, and if it is to be diagnosed early a much clearer concept of the condition will have to become widespread knowledge among the profession. However, it is extremely important that the diagnosis be made, because frequently it is the doctor who is unwittingly responsible for the patient's death.

The Syndrome

Porphyrics often have an apparently neurotic make-up. Many have complained for years about various pains, particularly in the abdomen. Because of these pains they often become drug addicts, taking barbiturates, aspirin, or a variety of patent medicines. They have usually seen many doctors, and unfortunately they may have had a number of abdominal operations. The urine is generally normal in colour, but, on questioning, patients may recall that their urine has been red during an illness in the past. The abdominal pain sometimes occurs in acute attacks accompanied by vomiting, when a diagnosis of appendicitis, intestinal obstruction, or some other abdominal emergency may be made. Patients, or some of the relatives, frequently have a skin that breaks down easily, forming blisters and then ulcers. This sensitivity of the skin is not usually apparent until adult life. The exposed areas of skin are particularly affected—the back of the hands and, in women, the front of the legs. Sunlight and minor injury appear to be precipitating causes. This ulceration is more common during pregnancy. The ulcers are usually small and multiple, and take a long time to heal. They are deep enough to leave permanent scars. Rather surprisingly, the ulcers of the skin are often most troublesome when the condition is quiescent, and may be absent during an acute attack. Conjunctivitis is a not uncommon symptom, and small pigmented spots that fluoresce in ultra-violet light may be seen in the retina.

During pregnancy the patient is usually much worse, perhaps partly because she is then given sedatives. There is often a history that previous pregnancies were terminated because of pains, vomiting, and hysteria.

In many cases a family group is first found to be porphyric when one of its members has an acute attack. More likely than not this acute attack follows an abdominal operation, particularly if thiopentone has been given as an anaesthetic, or it occurs during pregnancy. Women are more prone to be operated upon for lower abdominal pain than men; this fact and pregnancy probably account for