the appendage biopsy results failed to give any indication of prognosis. In two of our cases the comment had been made at the first operation that " it would not be surprising if the rheumatic process were still active," and in these two cases the appendage biopsies showed numerous Aschoff bodies suggesting continued rheumatic activity. Another patient had several attacks of subacute rheumatism in the interval between operations.

Logan *et al.* (1962) found that 36% of patients who had cusps completely separated anteriorly and posteriorly developed restenosis after an interval of more than five years.

This was not the experience of Belcher (1960, 1962), who found that only 4% of patients who had a complete split of both commissures had restenosed when followed up for eight years. Furthermore, he is convinced that an inadequate first operation is of prime importance in causation, and he has not known of restenosis in any case in which he has used the dilator.

Can these diverging views be reconciled? Before expressing an opinion several variable factors require to be considered, such as the critical assessment of operation notes, completeness of follow-up studies, criteria accepted for the diagnosis of restenosis, and the time interval between operations.

Our findings tend to support those of Belcher (1960, 1962). In 27 of the 32 cases the primary operation was undoubtedly inadequate. No case had a complete separation of both anterior and posterior commissures. We believe that after every valvotomy there is some re-fusion at the outer ends of the commissurotomy, and this is certain to occur. It would seem logical that a poor split followed by this inevitable restenosis would in most cases lead to a recurrence of symptoms. On the other hand, a similar amount of restenosis in a case having had a wide split would not decrease the size of the valve orifice by the same proportion. When we examined the decrease in valve size in the interval between operations we found that it amounted to 1 to 1.5 cm. in 23 (72%) cases, 2 cm. in 4 (12.5%), 2.5 cm. in 4 (12.5%), and 3 cm. in one case (3%). This possibility of inevitable reduction in value size, say from 1 to 1.5 cm., would explain our finding that stenosis recurred most often in cases in which the primary valvotomy was inadequate. When restenosis occurred in patients believed to have had a reasonable split the process had been more extensive (2 to 3 cm.).

Is this theory of inevitable partial re-fusion compatible with the common experience that many patients who have had an inadequate valvotomy make good progress and have no recurrence of symptoms for many years? We believe that in some cases it is possible that a degree of restenosis may occur without giving rise to symptoms, for it must be borne in mind that in some patients the actual valve stenosis may be the main or only feature, while in others the effects of prolonged back pressure and myocardial damage are so extensive as to bear a much greater influence on the result of any valvotomy carried out. In other words, there are two groups of patients—the one in which the size of the valve orifice is the dominant feature, and the one in which other factors are of equal or of more importance. Wood (1954) stressed that in the latter group the size of the valve orifice in mitral stenosis bore no relation to the liability to develop symptoms such as pulmonary oedema and auricular fibrillation.

Summary

In a series of 270 valvotomies the case records of 32 patients requiring reoperation have been reviewed.

In more than half the cases deterioration occurred within the first two years after operation. In several cases this deterioration was not sufficient to warrant operation for a further two years.

In all cases the valve orifice at the second operation was smaller than at the conclusion of the first, and in 11 the valve size was smaller than before splitting at the first.

The primary commissurotomy was regarded as inadequate in 27 cases.

It is suggested that after mitral valvotomy all cases develop some degree of re-fusion, and in consequence recurrence of symptoms is most likely in those that had an inadequate valvotomy.

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CUSHING'S SYNDROME AND SKIN PIGMENTATION

BY

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The role of the pituitary in Cushing's syndrome has been debated since the syndrome was first described (Cushing, 1932). Adenoma formation in the pituitary, found in 34 out of 58 cases collected by Knowlton (1953), is no proof of excess endocrine activity, as such tumours are not uncommon in the absence of adrenal dysfunction (Susman, 1935). A strong pituitary stimulus is suggested by the manner in which minute adrenal fragments may hypertrophy after adrenalectomy (Mason, 1957). Direct evidence of pituitary hyperfunction was provided by Clayton (1958) and Davies *et al.* (1960), who recorded high levels of plasma A.C.T.H. in Cushing's syndrome, although Paris *et al.* (1954) had previously reported negative results.

The relationship of Addisonian pigmentation to pituitary activity was demonstrated by Sulman (1956), who found raised concentrations of a melanophore-stimulating hormone (M.S.H.) in Addison's disease and also in some cases of Cushing's syndrome. The close similarity of M.S.H. and A.C.T.H. makes it impossible to determine the contribution of each hormone to the

total melanophore-stimulating activity present in blood (Harris and Lerner, 1957; Karkun *et al.*, 1960). Intense Addisonian type pigmentation has been recorded in untreated Cushing's syndrome associated with large pituitary tumours (Marks, 1959) and with similar tumours apparently arising after adrenalectomy (Nelson *et al.*, 1958; Bayliss, 1959). Skin pigmentation appears to be a clinical sign of pituitary overactivity.

This paper records the occurrence of pigmentation during the development or treatment of Cushing's syndrome and in the absence of adrenal insufficiency. Seven patients of a series of 21 who survived adrenalectomy for at least one year developed some pigmentation. One case presented with pigmentation and active Cushing's syndrome. Details of the eight cases are given in the Table.

Details of Cases

	Case 1	Case 2	Case 3	Case 4
Sex	Male	Female	Female	Female
Born	1908	1925	1937	1936
First seen	Oct., 1959	Nov., 1958	May, 1957	May, 1954
History	2 years. Obesity. Anginal pain. Hypertension. Skin darkening	1½ years. Obesity. Depression. Oligomenorrhoea	15 months. Obesity. Oligomenorrhoea. Hypertension	1 year. Obesity. Oligomenorrhoea. Plethora
Abnormal pigmentation	Moderate	None	None	None
X-ray pituitary fossa	Normal	Normal	Normal	Normal
Initial therapy	Pituitary stalk section	Adrenalectomy. 10% of one gland left	Total adrenalectomy	Subtotal adrenalectomy. 5% each gland left
Cure of Cushing's syndrome	Death	Yes	Yes	Yes, but relapse in Oct., 1955
Residual adrenal function	—	Normal	None	—
Subsequent course	Sudden collapse and death 24 hours after operation. Necropsy: severe myocardial ischaemia	Good health to date	Continued to require steroid therapy. Two normal pregnancies with healthy children delivered in July, 1960, and Feb., 1962	Feb., 1956, hypertrophied adrenal remnant removed. No subsequent return of adrenal function. Good health on small doses of cortisone. Normal pregnancy and normal delivery in May, 1960
Pigmentation	Moderate degree over face, hands, and buccal mucosa	Intense blue pigmentation of lips and slight browning of skin. Appeared 7 months after operation; has remained static	Generalized during pregnancy alone. Skin faded within 1/12 of each delivery	Minimal after second adrenal operation. Marked increase in pregnancy, but only limited fading after delivery
Serial *x*-ray films of pituitary fossa	—	Remained normal	Remained normal	Enlarged one year after pregnancy. No further enlargement to date
Plasma A.C.T.H.	23 milliunits/l.	—	—	—
,, M.S.H.	None detected	None detected	0·5 u./l. at 36/52 pregnant	2 u./l. at 38/52 pregnant
Other tests	Dexamethasone suppression test—positive	—	—	—
Pituitary histology	Acute infarction. Numerous Crooke cells. No tumour on serial section	—	—	—

Details of Cases—continued

	Case 5	Case 6*	Case 7	Case 8
Sex	Female	Female	Male	Female
Born	1931	1932	1900	1931
First seen	Feb., 1958	Nov., 1956	Sept., 1956	Feb., 1953
History	1 year. Obesity. Hirsuties. Amenorrhoea	8 months. Obesity. Hirsuties. Oligomenorrhoea	7 months. Obesity. Spontaneous fractures	2 years. Obesity. Hirsuties. Plethora
Abnormal pigmentation	None	None	None	None
X-ray pituitary fossa	Normal	Normal	Normal	Minimal enlargement
Initial therapy	Subtotal adrenalectomy. 10% of one gland left	Subtotal adrenalectomy, 10% of one gland left	Total adrenalectomy	Subtotal left adrenalectomy, leaving 20% of gland
Cure of Cushing's syndrome	Yes	Yes	Never complete	No
Residual adrenal function	None	None	Perhaps some, but cortisone dependent	Excessive
Subsequent course	Good health on steroid therapy	Good health with replacement therapy. July, 1958. Onset visual failure then right 3rd and 6th nerve palsies. Jan., 1959. D.X.T. to pituitary. Partial recovery of cranial nerves. No deterioration until Jan., 1961: Vision worse; cranial nerve palsies on right more marked. March, 1961: Removal of pituitary tumour. Improvement in vision and cranial nerves maintained	Some plethora and hypertension remained. Addisonian crisis if deprived of cortisone for 5 days. August, 1959: Signs of Cushing's syndrome. No ill effect from stopping cortisone. March, 1960. Pituitary stalk section. Remained well since. Some adrenal function still demonstrable but requires cortisone for good health	1956. Right total adrenalectomy. Subsequent Addisonian state dependent on cortisone until June, 1958. Signs of relapse of Cushing's syndrome. This progressed unchanged by D.X.T. to pituitary. Feb., 1960: Pituitary stalk section. Cure of Cushing's syndrome. Good health, requiring replacement therapy. Amenorrhoea; facial hirsuties continued when Addisonian, but disappeared after pituitary stalk section
Pigmentation	Intense from 4 months after operation. Did not fade when overdosed with cortisone for 2 months	Noticed 2 months after operation. Progressed to extreme degree by Dec., 1958. Slight fading after D.X.T., then even worse by March, 1961. Considerable fading after pituitary operation	—	Generalized but slight during phase of adrenal insufficiency. Progressive, especially of eyelids, with relapse of Cushing's syndrome. Complete disappearance after pituitary operation
Serial *x*-ray films of pituitary fossa	Remained normal	Normal Dec., 1957. Gross expansion Dec., 1958	Remained normal	Initial enlargement unchanged
Plasma A.C.T.H.	—	—	1·62 m.u./l. Feb., 1960	1·82 mu./l. Jan., 1960
,, M.S.H.	—	1·5 u./l. Dec., 1958	—	—
Other tests	—	—	Dexamethasone suppression—negative A.C.T.H. stimulation positive	—
Pituitary histology	—	Chromophobe adenoma, some basophil and acidophil differentiation. Mitotic activity suggests malignancy	Small basophil adenoma. No mitoses. Slight nuclear pleomorphism	Basophil adenoma. No mitoses. Moderate nuclear pleomorphism

* Initial history of Case 6 has been published by Schiller and Mason (1959).

Discussion

Plasma M.S.H. levels were measured in five patients: in three it was raised, and two of these were deeply pigmented. Plasma A.C.T.H. assays were performed in three cases, increased levels being found in all three. The highest value for plasma A.C.T.H. was found in a patient whose plasma M.S.H. was normal.

Hypophysectomy abolished the pigmentation in two patients. Addisonian skin pigmentation proved to be a reliable clinical guide to pituitary overactivity.

Skin pigmentation in the presence of adrenal hyperfunction was observed in three patients. The degree of pigmentation was not as intense as that observed in the four patients who became pigmented in the absence of functioning adrenal tissue. Localized pigmentation developed in only one patient whose adrenal function had been restored to normal by subtotal adrenalectomy. The persistence of pigmentation despite adequate steroid replacement therapy was in marked contrast to Addison's disease, in which pigmentation fades as replacement therapy becomes effective. The normal inhibiting effect of glucocorticoids on pituitary activity appears to be altered in Cushing's syndrome, but the limitation of pigmentation in the presence of adrenal hyperfunction suggests that the homoeostatic mechanism is insensitive rather than inactive. Williams *et al.* (1961) found that, for any blood level of hydroxycorticoids, the blood level of A.C.T.H. was higher in patients adrenalectomized for Cushing's syndrome than in patients with Addison's disease. Dexamethasone given in a dose sufficient to suppress normal pituitary function failed to suppress this activity in Cushing's syndrome, but suppression could be achieved by greatly increasing the amount of dexamethasone (Liddle, 1960).

Three pituitary tumours were detected in this series. Two were small non-invasive basophil adenomas associated with recurrent adrenal hyperfunction. One remained the same size for seven years. The third tumour, a chromophobe adenoma, grew rapidly and became locally invasive after the patient had been adrenalectomized. The speed of tumour growth appears to be slowed by the presence of excessive glucocorticoids and to accelerate if the glucocorticoid concentration is normal or low (Salassa *et al.*, 1959; Shrank and Turner, 1960).

Cushing himself noted that the small pituitary tumours associated with his syndrome were composed of basophil cells, but Marks (1959) pointed out that the large tumours, more rarely found, were usually chromophobe in type. Such chromophobe adenomas are very rich in A.C.T.H. (Bayliss, 1959; Montgomery *et al.*, 1959) and also differ from other chromophobe tumours in their propensity for local invasion causing cranial nerve palsies (Salassa *et al.*, 1959). Pituitary tumours in Cushing's syndrome maintain or increase their endocrine activity as they grow larger, but the cell type changes from basophil to chromophobe.

The growth of a pituitary adenoma, probably chromophobe and potentially malignant, should always be suspected if deep pigmentation is found in a patient with Cushing's syndrome, particularly if adrenalectomy has been performed. The small adenoma of basophil cells may not be detectable by radiological means, but it is suggested from the data on Case 7 that failure of dexamethasone to suppress adrenal function and successful adrenal stimulation by A.C.T.H. may be an indication of pituitary tumour formation.

The evidence cited above suggests that Cushing's syndrome in the absence of an adrenal tumour is caused by pituitary overactivity, which may be associated with tumour formation. The mechanism involved is the homoeostatic link between pituitary and adrenals; this link is deranged but not disrupted. Since there is ample experimental evidence, reviewed by Sayers (1960), to indicate that adrenal–pituitary homoeostasis is integrated by the hypothalamus, it is probable that Cushing's syndrome is primarily a disturbance of the hypothalamus, a view advanced by Heinbecker in 1944. Tumour growth in the pituitary does not argue against this hypothesis, as the limitation of such growth by excessive adrenal function indicates that the pituitary is not autonomous in terms of cell growth. Moreover, the hypothalamus has been shown to be essential for the histological differentiation of pituitary cells (Nikitovitch-Winer and Everett, 1958).

The evidence of pituitary overactivity in Cushing's syndrome and the occasional rapid growth of potentially malignant pituitary tumours after adrenalectomy call for a reappraisal of adrenalectomy as the treatment of choice. Destruction of the pituitary can be accomplished surgically or by radiation. In this series pituitary stalk section with partial removal of tumour tissue has proved effective and is a less severe surgical procedure than complete removal of the gland. Deep *x*-ray therapy to the pituitary has, in our experience, proved to be of little value in the treatment of Cushing's syndrome. It also failed to halt the growth of the large pituitary tumour in Case 6, although there was a temporary improvement. Implantation of radioactive materials into the pituitary offers a more reliable means of pituitary destruction, with minimal disturbance of the patient (Fraser and Joplin, 1961). However, pituitary ablation by any means causes a widespread disorder of endocrine function. The successful pregnancies recorded in this series would not have occurred if the patients had been treated by pituitary ablation instead of adrenalectomy. A therapeutic attack on the pituitary is recommended if the patient has Addisonian type pigmentation or any evidence, clinical or radiological, of a pituitary tumour. A relapse of Cushing's syndrome after initial cure by radical adrenalectomy also suggests that treatment should be directed to the pituitary rather than to the adrenal remnant.

Summary

Case records are given of eight patients with Cushing's syndrome who developed pigmentation at some stage of their disease and in the absence of adrenal insufficiency.

The presence and degree of pigmentation was found to be a reliable clinical guide to pituitary overactivity in terms of A.C.T.H. and M.S.H. secretion.

Pituitary tumours were demonstrated in three patients. The small tumours were benign functioning basophil tumours, but the one rapidly growing tumour, identical to others already recorded, was large, malignant, and chromophobe in type.

The rate of tumour growth and pituitary overactivity is diminished by excessive plasma hydroxycorticoid levels and enhanced when these levels are maintained at normal concentrations.

It is concluded that Cushing's syndrome is due to pituitary overactivity which is prompted by a hypothalamic disorder that disturbs rather than disrupts the normal homoeostatic link between pituitary and adrenal.

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REDUCING RADIATION HAZARDS IN THE RADIUM WARDS

BY

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Many authors have reported measurements of radiation dose received by hospital personnel, and some of them (Mayneord, 1951; Leetz, Masch, and Mohr, 1958; Clarke, 1960; Quimby, 1960; Zeitz and Zolg, 1960; Koren, Maudal, Flatby, and Berteig, 1960; Ellis 1961) have found, as we have, that one of the most difficult aspects of radiation safety in a hospital is the protection of ward nursing staff during the therapeutic use of radium. Large quantities of radioactive material are used, and such patients must receive nursing attention many times, under circumstances which prevent shielding according to laboratory standards.

Substantial radiation doses may be received in such circumstances, and official reports such as the Code of Practice (Ministry of Health, 1957) or the Recommendations of the International Commission on Radiological Protection (1960) give little help in reducing them.

During the past few years we have conducted a detailed study of this problem as it affects a ward in this hospital, where most gynaecological radium treatments are carried out.

Ward Routine

Ward nurses need to be near to the radium patient for the following procedures: (*a*) in theatre; during transfer of the patient to the ward, and during post-operative recovery; during removal of the radium at the end of treatment. (*b*) During radiographic localization. (*c*) During bed-making, washing, and care of pressure areas. (*d*) Attention to catheter, and emptying drainage. (*e*) During the taking of temperature, blood-pressure, pulse, and respiration rates; locker inspection. (*f*) Giving fluids and meals. (*g*) In emergencies such as vomiting and renewal of the catheter.

In the 10-bedded ward during the period covered by this survey about 60 radium treatments were given. It is not usual for more than one patient to be under treatment with radium at a time, but the precautions discussed below will still be applicable, *mutatis mutandis*.

Only on rare occasions in this ward, even at the start of the survey, has any member of the nursing staff received a dose as high as 300 mr in a week, or a total exceeding 1 r in 13 weeks. Even so, doses received during the nursing of radium patients were higher than those received by other nursing staff, and therefore (following the Recommendations of the I.C.R.P. that all doses be kept as low as possible) efforts have been made to reduce them.

The radiation received by the staff as a whole will depend partly on the nursing attention required by the patient, partly on the techniques used, and partly on the amount of radium inserted and the duration of treatment.

In order to eliminate these last two variables we have expressed the radiation received as milliroentgens per 1,000 milligram-hours of radium treatment; the total dosage received by the nursing staff during a period of over three years is shown, quarter by quarter, in Fig. 1. The radiation received has been evaluated separately for the sister in charge of the ward, her deputy (a staff nurse), and junior nurses, and these are shown in Fig. 2. A steady reduction is apparent, as is made clear in Table I.

Expressing doses in mr/1,000 mg. hours of radium treatment is of little value ordinarily, but it does enable

TABLE I.—*Radiation Records on a Radium Ward for a Period of Over Three Years (Doses in Milliroentgens per Thousand Milligram-hours of Radium Treatment)*

Measurements Made in	Total Radiation received by Nursing Staff	Radiation received per Person		
		Sister	Staff Nurse	Junior Nurses
1958	213	22	32	29
1959	187	12	25	21
1960	161	13	15	16
1961	78	7	14	10

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