HOSPITAL OUTBREAK OF CROSS- INFECTION DUE TO STAPHYLOCOCCUS PYOGENES PHAGE TYPE 80

BY

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The recent increase in cross-infection in hospitals due to antibiotic-resistant strains of *Staphylococcus pyogenes* is a matter of general concern. In Hitchin we have recently had experience of such an outbreak due mainly to a strain belonging to phage type 80. This strain has been responsible for two outbreaks in Australia (Rountree and Freeman, 1955; Taft, 1955) and gave rise to an epidemic in Southampton (Duthie, 1957). Records of epidemics of virulent staphylococci affecting whole hospitals are few, and include that in Southampton, one in Montreal which has been reviewed by Starkey (1956), and an outbreak in Calgary (Colbeck, 1949).

Our attempts to eliminate the infection by isolation, treatment of carriers, and hygienic measures in the wards, combined with reduction of admissions and closure of wards, have failed. The information acquired during this attempt and the factors which led to its failure seem worth publishing so that, perhaps, other workers may not have the same experience.

The Hitchin Hospitals comprise the Lister Hospital (256 beds), a hutted old E.M.S. hospital, with recent additions, and the North Herts and South Beds Hospital, brick-built with 116 beds. The two hospitals work as a single functional unit except for the maternity unit of 40 beds, which has its own staff, living and eating separately.

This paper describes the incidence and types of lesions due to tetracycline-resistant staphylococci from July, 1956, to July, 1958. The data for the first year were obtained from laboratory records and case notes; from July, 1957, to July, 1958, special records were kept day by day as the cases occurred.

For 11 weeks from the end of November, 1957, weekly nasal swabs from in-patients and staff were taken, this period covering the time of attempted wholesale clearance of the infective strains from the two hospitals. Records of the carrier rate of certain wards were also obtained for several months after clearing operations.

Bacteriological Methods

Wound swabs were taken in the usual manner with orange sticks tipped with cotton-wool. Anterior nasal swabs were taken with a platinum loop and immediately inoculated. Skin swabs were taken with a loop carrying peptone water, stroked several times over roughly 1 cm. of skin and inoculated.

Swabs from lesions were cultured on horse-blood nutrient agar and sensitivities to antibiotics tested with Evans "sentest" disks on the primary plate. Nasal and skin swabs were cultured on a similar medium

containing 10 µg. of tetracycline per ml. to suppress tetracycline-sensitive organisms. This method thus excluded from our study carriers of tetracycline-sensitive strains of *Staph. pyogenes*, limiting our identification of carriers to those bearing antibiotic-resistant strains. This technique allowed a small hospital laboratory to examine more swabs than would have been possible by the use of ordinary media. Neomycin sensitivities were determined by serial dilution in nutrient broth with subsequent culture to find bactericidal and bacteriostatic levels. *Staph. pyogenes* colonies were identified by colonial and morphological appearances and confirmed by slide and tube coagulase tests. Strains isolated from most lesions and some carriers were sent to Dr. R. E. O. Williams, who kindly determined the phage types.

Blankets were examined for their degree of bacterial contamination by shaking them hard twice and holding them for 20 seconds over exposed blood-agar plates and incubating for 18 hours.

Types and Incidence of Infected Lesions

The incidence of tetracycline-resistant staphylococcal lesions of all types in the different wards of the two hospitals and out-patient departments, and the number of cases transferred from other hospitals and of those apparently infected in general practice, are recorded in Table I on a monthly basis. For the last 11 months the numbers of phage type 80 strains are also given. The cases from the geriatric wards include both sexes, as do the figures for the various out-patient and casualty departments.

The male surgical ward at the Lister Hospital was most affected; this ward receives traumatic cases, emergency general surgery, and some cold general surgery and orthopaedic cases. The equivalent female ward was also affected, though less severely, as were the two medical wards. Fewer cases occurred at the North Herts Hospital, particularly after the cleaning operations. Apart from an improvement in the children's ward the attempts at wholesale clearing of the other wards failed to alter the incidence of infection at the Lister Hospital.

The anatomical pattern of infection in the different types of ward is shown in Table II. Primary infection of the skin, mostly minor, causing boils, furuncles, and whitlows in adults, and conjunctivitis and pemphigus in the newborn, accounted for 46% of all infections and 53% of all type 80 ones. Cross-infection of wounds caused the majority of other cases, although, as will be seen, in male medical wards secondary infection of the respiratory tract was frequent. The different pattern in the medical and surgical ward demonstrates the ease of colonization and subsequent infection of any abnormal anatomical site. Healthy nurses were infected only on the skin, although the numbers affected were high (31 of a total nursing staff of 215). Cases on the geriatric wards were few, possibly due to the fact that they were housed separately from the rest of the hospital and were nursed by a different and predominantly part-time staff.

Sources of Infection

Nearly all operation wounds were found to be satisfactory for the first few days and at the first dressing. In only three cases were the wounds discharging or breaking down at the first dressing. The cases in the male surgical ward at the Lister

TABLE I.—Incidence of Lesions due to Tetracycline-resistant *Staph. pyogenes* (phage type 80 in parentheses) from July, 1956, to June, 1958

	Average Daily Beds Occupied	Average Monthly Admis- sions	J	A	S	O	N*	D*	J*	F*	M	A	M	J	Total	
															No.	Phage 80
Lieter hospital:	23	72	6	1	1	3	3	1	1	1	1	1	1	1	45	30
Male surgical	23	69	3	1	1	1	1	1	1	1	1	1	1	1	15	15
Female "	18	51	2	1	1	1	1	1	1	1	1	1	1	1	22	17
Male medical	22	55	1	1	1	1	1	1	1	1	1	1	1	1	28	17
Female "	21	70	1	1	1	1	1	1	1	1	1	1	1	1	18	12
Mixed male med. and surg.	13	80	1	1	1	1	1	1	1	1	1	1	1	1	12	8
Children															17	8
N. Herts Hospital:	20	65	1	1	1	1	1	1	1	1	1	1	1	1	14	5
Male surgical	42	123	2	2	2	2	2	2	2	2	2	2	2	2	14	5
Female "	61	189	2	2	2	2	2	2	2	2	2	2	2	2	12	3
Gynaecological															13	7
Maternity unit																
Lieter hospital: Male and female geriatrics	52	71	0	0	0	0	0	0	0	0	0	0	0	0	9	6
Both hospitals: Out-patients cross-infected			1	2	10	2	4	1	1	4	3	2	0	0	27	17
Cases derived from other hospitals			0	0	0	0	0	0	0	0	0	0	0	0	11	4
General practice. No hospital contact			1	0	0	1	0	0	0	0	0	0	0	0	17	10
			22	13	22	22	14	11	22	26	26	39	16	18	245	144

* Ward clearance.

Hospital had many more infected wounds than the surgical patients in the mixed medical-surgical ward, although the operating theatre and team were the same for both wards. It thus seems likely that these wounds were nearly all cross-infected in the ward.

The primary skin infection and the secondary respiratory tract cases undoubtedly acquired their infection in the ward, confirming the extent of cross-infection in the hospital as a whole.

Auto-infection was difficult to prove in spite of extensive pre-operative swabbing, but two known nasal carriers of tetracycline-resistant strains were operated on and became infected at the operation site with a similar antibiotic-resistant strain.

Measures Taken to Reduce Cross-infection

From November 30, 1957, to February 8, 1958, each ward in turn was cleared by the technique of Shooter *et al.* (1957), except that the detergent-antiseptic mixture "deogen" was used instead of sodium hypochlorite and the walls, ceilings, and floors were washed and not sprayed. The furniture and loose equipment were similarly washed and the ward was reopened. As routine measures, bedpans, baths, and washing-bowls were disinfected or steam-sterilized after use. Examination of 12 dirty blankets from the wards by the technique described above yielded a mean growth of 715 colonies per plate, including some *Staph. pyogenes*. After hospital washing with detergent the plates yielded a mean growth of 3.5 colonies, indicating that routine laundering was effective. Hexachlorophane soap and 1% chlorhexidine hand-cream were used by the staff in the wards. Nasal carriers among the patients and staff were treated with antibiotics intranasally as suggested by Gould and Allan (1954) and Gould (1955), except that the antibiotic used by us was neomycin. A little ointment containing 0.5% neomycin sulphate was squeezed into the anterior nares three times daily for five days and once daily for a month. The carriers among the nurses were advised to change their personal linen and bed clothes frequently. Carriers among the patients were bathed or blanket-bathed three times daily with frequent linen changes and daily hair-washing.

Persistent nasal carriers among the staff and some patients were investigated more thoroughly by repeatedly swabbing five sites on the skin to determine the extent of skin carriage and the need for special treatment. Proved extensive skin carriage was treated

TABLE II.—Distribution of Cases According to Type of Lesion for an 11-Months Period

	Wound	Urine	Secondary Respiratory Tract	Primary Respiratory Tract	Secondary Skin Lesion	Primary Skin Lesion	Other Primary Sites
Staff	0	0	0	0	0	30 (20)	1 (0)
Male surgical	34 (25)	13 (7)	4 (3)	0	1 (1)	14 (13)	0
Female "	16 (8)	4 (1)	2 (2)	0	0	9 (9)	0
Male medical	2 (2)	2 (0)	9 (4)	2 (2)	1 (1)	17 (10)	0
Female "	1 (0)	3 (2)	0	2 (1)	0	9 (9)	0
Children	1 (1)	0	4 (2)	1 (0)	2 (1)	7 (6)	2 (0)
Male geriatric	0	0	3 (1)	0	0	3 (2)	0
Female "	0	0	0	0	0	3 (3)	0
Maternity unit	4 (3)	0	1 (0)	0	0	10 (3)	0
Accident service	10 (8)	0	0	0	5 (3)	7 (6)	1 (0)
General practice	1 (1)	0	2 (0)	0	2 (1)	11 (8)	0
Transferred from other hospitals	1 (0)	1 (0)	5 (1)	0	1 (1)	3 (2)	0
Total	70 (48)	23 (10)	30 (13)	5 (3)	12 (8)	123 (93)	4 (0)

N.B.—Primary skin lesions include breast abscesses and neonatal conjunctivitis. Other primary infections include osteomyelitis, intestinal, and vaginal infections. Phage type 80 in parentheses.

by repeated baths with hexachlorophane soap, frequent changes of underclothes, and the application of 1% chlorhexidine cream to the whole body, especially the axillae and perineum, and the continued use of neomycin ointment intranasally.

After a ward had been cleaned and reopened only nurses who were known not to be nasal carriers were allowed inside it, and staff visiting it for any purpose whatsoever had to be known non-carriers. Patients transferred from elsewhere in the hospital were swabbed before transfer, but patients admitted direct from general practice were not swabbed before admission. Weekly nasal swabs were taken from staff and patients after reopening the wards. Patients who developed septic lesions infected with a tetracycline-resistant *Staph. pyogenes* were removed at once to an isolation ward of 13 beds and at first nasal carriers were also removed. The isolation ward became full and the pressure of emergency work prevented the closure of an additional ward to take the rest of the carriers. These were therefore energetically treated in the clean wards and persistent carriers transferred to the isolation ward as beds became available.

Results

Carrier State: Nurses

Swabbing of nurses in November, 1957, revealed a higher carrier rate than had been demonstrated in trial swabbings in June and September; on December 6 there were 51% nasal carriers among the nurses in the wards. The various measures adopted led to a rapid and substantial reduction in the carrier rate, as shown in the Chart. Twenty-four ward staff had detailed skin

Weekly incidence of nasal carriers of tetracycline-resistant *Staph. pyogenes* among patients and nursing staff. Carriers treated with intranasal neomycin ointment after December 6, 1957. Non-carriers not treated.

swabs taken, either because they had septic lesions in which there were tetracycline-resistant staphylococci or because they were found to be persistent nasal carriers. It was found that the presence of an infected lesion or a persistent nasal carriage in a nurse makes skin carriage probable; only five of the nurses selected for this swabbing as possible "skin spreaders" were in fact proved not to be so. Of 17 skin carriers treated and followed up, 16 were clear of infection within four weeks, most being clear in one week. In spite of intensive local treatment and systemic novobiocin 1 g. daily for five days, one carrier continued to be positive,

usually on several skin sites, for three months before she became clear, apparently spontaneously.

These swabs were taken from the anterior hair line, one axilla, the perineum, and from under the great toe by the technique described. Sometimes only one skin site was positive, at other times several or all in any combination or sequence as shown in Table III.

TABLE III.—Distribution of Skin Carriage Among 26 Members of the Staff, 18 Having Lesions and 8 Being Persistent Nasal Carriers

Lesion, but no nasal or skin carriage	0
" with nasal but not skin carriage	4
" with no nasal carriage but one skin site positive	2
(one of these was carrying on the perineum, one on the toe)	
Lesion with nasal carriage and skin carriage in at least one site	12
Perineum positive in 8, axilla in 8, toe in 7, and hair in 7)	
Persistent nasal carrier but no skin carriage	1
" carriers with skin carriage in at least one site	9
(Perineum positive in 5, axilla in 1, toe in 4, and hair in 1)	

Of 32 medical staff under weekly supervision for three months at one time or another, 10 had positive nasal swabs. They were advised not to operate or do dressings, were not allowed in the clean wards, and were treated as were the nasal carriers among the nurses. All yielded negative swabs after a few days' treatment and returned to work, continuing to use neomycin ointment. Of 115 administrative, clerical, and maintenance staff, only nine nasal carriers were found during four weeks' weekly swabbing, which was then discontinued. One of these, however, was persistent, and subsequently developed a boil due to a phage type 80 strain.

Carrier State: Patients

The carrier rate among the in-patients dropped at the same time as that of the nurses but did not reach such a low level. The changes at weekly intervals are also shown in the Chart. Of the 1,927 swabs taken from patients during the 11-weeks period, 281 (14.6%) were positive. Of the 195 patients who were positive at one time or another, 109 (56%) were so on first examination. Many of these were in hospital for less than three weeks, and these have been regarded as "short-stay" patients. Those having three or more swabbings have been regarded as "long-stay," and it has been possible to obtain some information on the persistence of their carrier state. Those having at least three positive swabs in any five-weeks period have been regarded as persistent. Other patients have had isolated positive swabs with several negative ones. These occasional carriers have usually been positive only on first weekly swabbing and after neomycin treatment, not again. Sometimes positive swabs have been obtained within 12 hours of admission, we think probably from infection in the ward, as a trial swabbing of 100 consecutive patients before admission to the ward yielded no carriers.

Table IV shows the numbers of short- and long-stay carriers with their persistence and any associated infected lesion.

TABLE IV

	Nasal Carriage	Total	With Lesions
Short-stay patients ..	Negative	609	13
	Positive	88	5
Long-stay ..	Negative	154	11
	Occasional	83	7
	Persistent	21	2

Not unexpectedly, the longer an admission the greater the probability of any one patient becoming a carrier. The high proportion of positives on first swabbing, with fewer on subsequent occasions, is likely to be due to the

effect of intranasal neomycin ointment, but, as Table IV shows, sporadic acquisition of nasal carriage among long-stay patients is frequent. The 21 persistent carriers were energetically treated with all the measures described above, none, however, being converted to a carrier-free state. On the other hand, 24 patients with infected lesions never became nasal carriers.

After clearing the wards sporadic nasal carriers reappeared among the patients during the next few weeks. The patients transferred to these clean wards were proved not to be nasal carriers before transfer, but it was shown that they provided the source for reinfection of the clean wards either by skin carriage or from an unidentified staphylococcal lesion, most often low-grade bronchitis. In view of the failure of the general attempts at reducing cross-infection, on the advice of Dr. R. A. Shooter and Dr. R. E. O. Williams all the staff and patients of the two surgical wards at the Lister Hospital were treated with neomycin ointment intranasally. This was continued three times daily for six weeks whether the patients and staff were carriers or not, and the incidence of carriers and lesions was compared with those in the two medical wards. The results of this experiment are shown in Table V, in which it is apparent that, in the heavily infected male surgical ward at least, no advantage was to be gained by the treatment.

Infection Among Out-Patients

Cross-infection of tetracycline-resistant staphylococci has been frequent in the hospital out-patient department throughout the two-year period. Cases discharged from the wards are dressed in the out-patient department and provide continuing foci of infection there. Patients previously infected in general practice were infrequent until January, 1958, since when 15 cases have occurred, 10 of which were of phage type 80. Infected cases from other hospitals were also rare until the same time, but nine have been seen since. These two additional sources for antibiotic-resistant strains have further increased the difficulties of controlling cross-infection. Cases identified before admission were received into the isolation ward, attempts being made to determine the bacteriology of infected lesions wherever possible. Two patients with minor septic lesions not included in the Chart were infected by contact with a known infected patient discharged from hospital.

Phage Types and Antibiotic Resistance

Throughout, the investigations were concerned only with tetracycline-resistant *Staph. pyogenes*. Tetracycline-sensitive strains were infrequently isolated except from swabs received from septic lesions infected outside the hospital, and those that were found were ignored from the point of view of control of infection. All the tetracycline-resistant strains were also resistant to penicillin and many were also resistant to

streptomycin. Out of the 309 strains submitted for phage-typing, 213 belonged to group I (198 were type 80), 8 were group II, and 88 were group III. The latter included 10 erythromycin-resistant strains, most of which were phage type 75/77. No strains resistant to chloramphenicol, novobiocin, vancomycin, or neomycin were found. Strains isolated from six nurses with persistent nasal and skin carriage who had been treated with neomycin intranasally were all sensitive to neomycin (bacteriostatic at 1.25 µg./ml., bactericidal at 1.25 to 5 µg./ml.), and no resistant strains were found from the wards in which all patients and staff were treated with this antibiotic.

Discussion

In order to reduce cross-infection between patients it is necessary to review the sources of infection, the depots in which the infecting organism may persist, and the means of their conveyance (Starkey, 1956). Our attempts at the control of cross-infection in the Hitchin Hospitals were concerned with these three sets of factors simultaneously. The distribution of infection was heavy and widespread enough to necessitate these attempts in the two hospitals as a whole.

The methods of cleaning the wards and their equipment have been used in previous outbreaks of cross-infection in other hospitals. The review of nursing procedures in the wards revealed no major flaws in hygiene, and the measures introduced are believed to be as satisfactory as could be hoped for, considering the density of beds and the pressure of work in a hospital dealing mainly with emergency admissions.

The failure to reduce the incidence of cross-infection in all its forms after considerable upheaval of hospital work was disappointing. The initial drop of the carrier rate among patients and staff had been encouraging, and it seemed that the persistence of a few nasal and skin carriers with the presence of unidentified infected lesions provided foci for further spread. Our investigations of the ward recurrences after cleaning suggest that both these factors play a part, often together.

Intranasal neomycin ointment appeared to be effective for the majority of nasal carriers among the staff, although some persistent carriers remained despite treatment vigorously applied. Both intranasal and skin treatment were less effective among the patients, nasal carriers continuing to appear during the six-weeks trial of intranasal neomycin in all carriers and non-carriers. Persistent carriers among the patients were particularly difficult to clear, and we think that this difference between the results of treatment among nurses and patients was due to the density of infection in the wards and the greater chances of reinfection to those who are continually within them. Our experience of investigating recurrence of infection after cleaning wards convinces us that, under the conditions of busy

TABLE V.—*Number of Patients Swabbed (a), the Number of Nasal Carriers Found (b), and the Number of New Lesions Occurring Weekly (c), During a Six-weeks Trial of Neomycin Treatment, Starting March 30, 1958. Carriers and Non-carriers all Treated*

[illegible]

medical and surgical work, barrier-nursing in a side-room is ineffective. The barrier-nursing included the use of gowns, but patients were attended by any member of the staff on duty, as was done in the investigation of spread of staphylococci in a surgical ward at St. Bartholomew's Hospital by Shooter *et al.* (1958). These workers, however, found barrier-nursing effective.

The initial determination of the carrier rate provides evidence of the density of infection among patients and medical, nursing, and lay staff, and may indicate the lines along which preventive measures should be directed. Subsequent swabbing identifies carriers to be treated with neomycin. It will identify persistent carriers, on whom detailed skin swabs may show widespread carriage and an accompanying danger of dispersal. Our findings are in agreement with those of Hare and Ridley (1958) in suggesting that the perineum in both sexes is a potent source of staphylococci.

Once neomycin treatment has been instituted the density of nasal carriage, or its absence, does not indicate the likelihood of infected lesions occurring. The tedious procedure of weekly nasal swabbing throughout a hospital is therefore of practical value only if the carriers so identified can be isolated. Owing to shortage of nurses and wards and the pressure of emergency work, even during a period in which all routine admissions were stopped, it was impossible to provide sufficient isolation beds to do this. We feel that in so widespread an epidemic no measure short of an isolation policy of this magnitude is likely to do more than reduce the incidence of infected lesions.

In the first six months of 1958 it became clear that there was an increasing depot of infection of tetracycline-resistant strains, including phage type 80, in the population of the area. Some of this had been derived from the epidemic in the Hitchin Hospitals, some from other hospitals, and 17 cases had no determinable contact with hospital infection.

Although the majority of infections with strains of phage type 80 that we have seen had been mild, a few severe cases, including one of peritonitis after laparotomy and one of septicaemia with a carbuncle in a nurse, show that this is not always so. Most of the minor lesions have been primary skin infections such as boils, small spots, and carbuncles. The strain was first identified by Rountree and Freeman (1955), when it was isolated from skin lesions, and it appears to have an unusually great tendency to colonize normal or abnormal skin. In old and debilitated people this strain may produce severe bedsores and infect the lungs, being partly or wholly responsible for a terminal bronchopneumonia. Clinically, the strain appears both more virulent and more invasive than other group I or group III strains, but experimental evidence of this increased virulence is lacking (Elek and Conen, 1957).

Widespread infection of a hospital with this strain leads to increased risks to patients admitted for any reason whatsoever and results in an increase of septic lesions among nurses. Attempts to eliminate the infection from the hospital have failed and cases of cross-infection continue to appear. It is felt that no measure short of reduction of emergency work as well as routine admissions would provide enough isolation beds to remove carriers as well as patients with lesions, and that, with foci of infection in the population of the area, elimination of the infection is not a practicable proposition.

Summary

A hospital epidemic of cross-infection due to *Staphylococcus pyogenes* phage type 80 is described.

Attempts at wholesale elimination of the infection were undertaken and failed.

Inability to isolate carriers as well as patients and staff with infected lesions appeared to be a major factor in the failure to eliminate phage type 80 strains.

High initial carrier rates among patients and staff improved after treatment, but there continued to be some persistent nasal and skin carriers in spite of treatment.

Foci of infection of phage type 80 and other tetracycline-resistant strains are increasing in the population in general practice, and it has proved necessary to provide isolation facilities for these cases identified before admission.

We are indebted to Dr. R. E. O. Williams and Dr. Patricia Jevons for determining the phage types and to them and Dr. R. A. Shooter for much advice. We thank the medical staff, the matron and nursing staff, and the hospital secretary, Mr. B. D. M. Smith, for wholehearted co-operation in our attempts at controlling this infection, and in their forbearance in the disruption of hospital life involved.

REFERENCES

- Colbeck, J. C. (1949). *Canad. med. Ass. J.*, **61**, 557.
 Duthie, E. S. (1957). In *Hospital Coccal Infections*, edited by R. E. O. Williams and R. A. Shooter, p. 23.
 Elek, S. D., and Conen, P. E. (1957). *Brit. J. exp. Path.*, **38**, 573.
 Gould, J. C. (1955). *J. Hyg. (Camb.)*, **53**, 379.
 — and Allan, W. S. A. (1954). *Lancet*, **2**, 988.
 Hare, R., and Ridley, M. (1958). *Brit. med. J.*, **1**, 69.
 Rountree, P. M., and Freeman, B. M. (1955). *Med. J. Aust.*, **2**, 157.
 Shooter, R. A., Griffiths, J. D., Cook, J., and Williams, R. E. O. (1957). *Brit. med. J.*, **1**, 433.
 — Smith, M. A., Griffiths, J. D., Brown, M. E. A., Williams, R. E. O., Rippon, J. E., and Jevons, P. (1958). *Ibid.*, **1**, 607.
 Starkey, H. (1956). *Canad. med. Ass. J.*, **75**, 371.
 Taft, L. I. (1955). *Med. J. Aust.*, **2**, 970.

FLUOXYMESTERONE

A NEW ORAL ANDROGEN

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Male hypogonadism, be it primary, or secondary to hypopituitarism, requires androgen therapy, and treatment has become possible as the result of the synthesis of testosterone from cholesterol (Ruzicka and Wettstein, 1935; Butenandt and Hanisch, 1935). Initially, intramuscular injections of free testosterone three to seven times a week were employed. Subsequently, derivatives have been synthesized in an endeavour to produce more potent androgenic activity and a longer duration of action. Testosterone propionate in oily solution required to be injected intramuscularly only two to three times a week; crystalline suspensions were developed for injection every one to two months; and solid implants of testosterone or the propionate required insertion every three to four months (Miescher, Wettstein, and Tschopp, 1936; Deanesly and Parkes, 1937; Foss, 1937; Biskind, Escamilla, and Lissner, 1941). The disadvantage of these preparations is that they are largely inactive when taken by mouth, owing to their destruction by the liver.