Summary

The differences occurring in the composition of milk on the seventh day of lactation have been studied in 150 women, 121 of whom were primiparae.

There is no statistically significant difference between the milk of primiparae and multiparae in this series, but evidence is presented to show that the same individual, in two lactations, may produce milk differing greatly in fat content.

There is a wide range of values for all the major constituents as well as for the total yield at this stage of lactation. The variability of the lactose and protein seems to be due to differences in speed of maturation of the milk.

There is a wide range of fat content, and consequently of calorie value. The fat content is not apparently related to the content of other constituents, and seems to be an individual characteristic. In some milks the fat content is so low that, even with a high milk volume, the child may be undernourished.

I am grateful to Professor Dugald Baird and to the staffs of the Midwifery Department and the Aberdeen Maternity Hospital for invaluable help; to Dr. I. Leitch, of the Commonwealth Bureau of Animal Nutrition, Bucksburn, for criticism and advice; and to Dr. F. H. C. Marriott for statistical assistance.

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IODODERMA OF THE FACE AND MARKED EOSINOPHILIA

BY

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Iodine has a long-established place in the history of medicine. There are few drugs which have been used more freely in the treatment of coughs, syphilis, and thyrotoxicosis, apart from its popularity as a skin disinfectant. Relatively few cases of iodism have been reported despite the commonness of its use and importance in radiological contrast substances.

The present case draws attention once again to the dangers of iodine intoxication and demonstrates two features of some interest—an unusual skin lesion and a pronounced eosinophilia.

Case Report

A 60-year-old white man of French extraction, resident in British Columbia for over 30 years, was admitted to the Vancouver General Hospital on February 27, 1952. Asthma had troubled him at infrequent intervals for many years without producing any severe disability. During 1951 he had two major surgical procedures—a suture of a perforated gastric ulcer in April and a transurethral prostatectomy in November—and during this period his general health deteriorated and his asthma became increasingly severe.

In October, prior to his prostatectomy, he was submitted to intravenous pyelography, and developed a severe but temporary reaction to the iodine-containing contrast substance. In November, for a four-week period following his operation, he was given 5 gr. (0.32 g.) of potassium iodide three times a day in an attempt to avoid any fibrous con-

traction of the prostatic bed. During January, 1952, his asthma became more troublesome. Towards the end of the month he treated himself with proprietary asthma tablets, each containing about 1½ gr. (0.1 g.) of potassium iodide. He took an average of six tablets daily. A few days after beginning this treatment he noticed red vesicular raised spots appearing on his arms and trunk. He described them as being like "pimples from which no pus came." By the middle of February he had developed several spots on each malar region, and these gradually spread and coalesced to form fungating tumour-like masses. These lesions and his severe asthma caused his admission to hospital.

Physical examination on admission showed a firm raised reddish mass with an irregular surface over each malar region of the face; severe asthma with an emphysematous chest; hypertension (B.P. 190/108); and a few vesicular spots on the upper trunk and arms.

Laboratory studies on February 28 showed: Hb, 97%; W.B.C., 32,950 (P. 22%, staffs 1%, lymphs 6%, monos 4%, eosins 66%, basophils 1%); N.P.N., 38 mg. per 100 ml. Urinalysis: Sp. gr. 1022; protein +++; W.B.C. ++; R.B.C. ++; and an occasional hyaline cast seen.

During the week February 28 to March 6 the patient's condition steadily deteriorated and oxygen was given continuously. Treatment included adrenaline, aminophylline, penicillin, and potassium iodide—5 gr. (0.32 g.) three times a day. Bacteriological examination of the facial lesions on three occasions revealed the presence of only coagulase-negative *Staphylococcus albus*.

A sternal puncture and haemogram were performed on March 4, the findings being:—(1) Peripheral blood: Hb, 98% (14.2 g.); R.B.C., 5,300,000; platelets, 350,000; reticulocytes, 1%; haematocrit, 44%; W.B.C., 31,800 (neut. polys 16%, neut. staffs 2%, eos. polys 55%, eos. staffs 15%, lymphs 8%, monos 4%). (2) Bone marrow: On a 300-cell differential count 37.3% were lobed eosinophils, 11.3% staff eosinophils, 4.3% metamyelocyte eosinophils, 5% myelocyte eosinophils, and 0.6% promyelocyte eosinophils. The marrow was not as hypercellular as one would expect in a leukaemic condition, and in view of this, the absence of splenomegaly, and the excessive rarity of eosinophilic leukaemia it was felt that the latter was probably not the diagnosis.

On March 6 the patient was seen with a view to the possible administration of A.C.T.H. as a life-saving measure. His condition was critical. The striking lesions on the face had extended and the surface was now a blackish-red colour (Fig. 1). He was in an oxygen tent, his breathing was asthmatic and very laboured and noisy, and he was roused only with difficulty, his answers to questions being irrational. In addition to hypertension he had a marked tachycardia (pulse rate 160) with numerous extrasystoles. Examination of the upper trunk and arms revealed the presence of numerous rounded raised red papular spots of varying size, while similar spots were evident on the chin and ears.

The patient was put at once on intravenous A.C.T.H., digitoxin, pethidine hydrochloride, and diphenhydramine hydrochloride, the pre-

FIG. 1.—Photograph of patient showing facial lesions.

vious drug treatment being stopped. After 48 hours under this regime he showed marked improvement, oxygen was discontinued, and a steady uneventful recovery was made.

The day following the change in treatment the full story of iodine intake was obtained and the diagnosis made of iododerma, the facial lesions being typical of some previously described in this condition.

A biopsy from one of the facial lesions was taken. The pathologist reported: "The surface of the lesions is covered by hyperkeratosis and parakeratosis. Extending deeply into the underlying cutis there is marked epitheliomatous hyperplasia with both large and small epithelial pearls. In the centre of many of the smaller projections are minute micro-abscesses. Despite this irregular and marked acanthosis, however, the constituent cells are well differentiated and prickle-cell bridges can be demonstrated. Nowhere does the lesion suggest cytologically a squamous-cell carcinoma, though the picture superficially is somewhat similar. The dermis in both the superficial and deeper parts of the lesion suggests a fibrosis and is heavily infiltrated with subacute and chronic inflammatory cells. The picture is consistent with a diagnosis of iodism."

In all only 85 mg. of A.C.T.H. was given intravenously over a period of eight days, the infusion being kept going almost continuously. The effect of the A.C.T.H. on the eosinophils and 17-ketosteroids is illustrated in Fig. 2.

FIG. 2.—Showing effect of A.C.T.H. on 17-ketosteroid excretion and eosinophils.

During the recovery period the facial lesions slowly regressed. The asthma improved greatly without being completely relieved, while the pulse rate fell to between 80 and 90. The albuminuria remained +++ for about a week, and then gradually subsided, only a trace of albumin being noted on March 20, the day before discharge.

The patient was readmitted three weeks later for further study. At that time his total eosinophil count was about 1,000 per c.mm., his asthma was still troublesome, but the facial lesions had completely disappeared apart from some slight residual pigmentation of the skin. There was no albuminuria.

Comment

This case presents several unusual features which stimulate speculation on the mechanisms involved. Reactions to drugs can be broadly divided into two types; (1) toxic

signs and symptoms due to acute or chronic overdosage; and (2) signs and symptoms due to a personal idiosyncrasy producing hypersensitivity to the drug. In this particular case there are features of both types of reaction. The vesiculo-papular rash and tumour-like masses are recognized features of iodism due to chronic intoxication with the substance, while the sharp reaction to the pyelography and the very high eosinophilia of the later acute illness both suggest a hypersensitivity type of reaction. It is interesting to note that two months after the reaction to the pyelography a four-weeks course of potassium iodide produced no obvious symptoms, but after the beginning of the second course, six weeks later, the rash appeared almost immediately. The first course appeared to be a "sensitizer" which resulted in a hypersensitive response to the second. Seymour (1937) reported a similar effect with iodine applied to the skin. A 7.5% tincture was used for the skin preparation for the induction of an artificial pneumothorax. After the sixth treatment a rash developed which settled in a few hours. Eleven days later the procedure was repeated, and within a week the patient was dead from an exfoliative dermatitis.

The marked eosinophilia in the present case supports the idea of a sensitivity reaction. The patient was susceptible to allergic manifestations, being a chronic sufferer from asthma. As such he may have had a moderate eosinophilia for years, but the level of the eosinophils in the blood in this acute illness was much higher than normally found in asthma *per se*. Iodine in the blood stream is largely bound to protein. "Foreign protein" is regarded as exerting a "chemotactic stimulus" to the production of eosinophilia (Whitby and Britton, 1947). One may postulate, therefore, that in this hypersensitive individual the iodine-protein complex has acted as a "foreign protein."

During the past 20 years two clinical entities have been described in which asthma and extreme eosinophilia are the main features. These are Löfller's (1936) syndrome and tropical eosinophilia. Apley and Grant (1945) thought there was a good case for classifying them under the one heading "eosinophilia with pulmonary disease" or the "E.P. syndrome." Two cases of this syndrome have been reported due to chronic brucellosis (Elsom and Ingelfinger, 1942). Herbert *et al.* (1950) have observed a difference between the two conditions in their response to A.C.T.H. therapy. The present case also shows the main features of the syndrome, and a clear aetiology. It supports the suggestion that the "E.P. syndrome" is probably a non-specific response to a variety of different hypersensitive conditions.

It is difficult to assess the role of A.C.T.H. in this patient's recovery. It seems possible, however, that the hormone did accelerate it. It is of interest to observe the satisfactory response to relatively small amounts of A.C.T.H. administered by slow and almost continuous intravenous infusion. In a previous paper (Cape *et al.*, 1952) it was shown that the minimum intravenous dose of A.C.T.H. given in this way which produced a maximum effect on the eosinophils was about 0.2 mg. per hour. Approximately double this dose was given in the above case with entirely satisfactory results. The fact that this dose will not produce a maximum stimulation of adrenal steroid production suggests that adequate therapeutic responses may be obtained without such full stimulation. The effect on the peripheral eosinophils was dramatic, as in less than 48 hours the count had fallen to 19 per c.mm. from almost 9,000. (See Fig. 2.)

After stopping A.C.T.H. the eosinophils rose to a level varying between 600 and 1,000. This level appeared to be fairly stable, as on the second admission three weeks later it was 1,000. This is consistent with the eosinophilia seen in chronic asthmatics and suggests that this patient did normally have an increased level of the cells in his blood.

The significance of the urinary findings in the acute stage of the condition was not entirely clear in view of the previous history of prostatic trouble. However, older records showed that, while some white cells and a trace of

protein were present in the urine following the prostatectomy, no red cells were found. This and the manner in which the urinary abnormalities cleared up during the recovery period indicate that the iodism was accompanied by a moderately severe degree of an acute renal disturbance, part of a generalized allergic reaction.

Summary

A case of iododerma, with striking facial lesions, is described. The patient was a severe asthmatic treated, *inter alia*, with potassium iodide. Hypersensitivity to the iodine resulted in skin lesions, a marked eosinophilia, tachycardia, and proteinuria.

Recovery followed the withdrawal of iodine and the administration of A.C.T.H.

The mechanism of the intoxication is discussed with particular reference to the significance of the eosinophilia. A comment is made on the so-called "E.P. syndrome" and on the effect of A.C.T.H. in the recovery of the patient.

I would like to thank Dr. A. S. Turner for permission to publish this case, and Dr. R. A. Palmer, director of the metabolic unit, Vancouver General Hospital, for his stimulating advice and criticism.

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PRE-ERYTHROCYTIC STAGES OF HUMAN MALARIA: PLASMODIUM OVALE

A PRELIMINARY NOTE

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Four species of malaria parasites are found in man—*Plasmodium vivax*, *P. falciparum*, *P. malariae*, and *P. ovale*. Pre-erythrocytic stages of *P. vivax* were demonstrated by Shortt *et al.* (1948) and of *P. falciparum* by Shortt *et al.* (1949) and Jeffery *et al.* (1952). Elucidation of this cycle in the remaining types presents two special difficulties: (1) the comparative rarity of the parasite, and (2) the poor infections usually obtainable in mosquitoes (an essential factor for success of an experiment of this kind is a large supply of heavily infected mosquitoes). Fortunately, *P. malariae*—the agent responsible for quartan malaria—has a replica in monkeys, *P. inui*, which in length of blood cycle (72 hours), length of infection in mosquitoes, and morphology closely resembles the human form; and the demonstration by Garnham (1951) of the tissue cycle of *P. inui* probably indicates the nature of the pre-erythrocytic stage of *P. malariae*. No such simian counterpart exists

in the case of *P. ovale*, and a human experiment was necessary if the problem were to be solved. A further practical difficulty to-day is the scarcity of cases of general paralysis in need of malaria therapy; practically none were available for this experiment, and, except for a short break when the infection was kept at Horton Mental Hospital, the strain had to be maintained amongst ourselves. The strain was obtained from Dr. A. R. D. Adams, who had originally isolated it from a patient from Liberia and had passed it through two patients by blood transfer before sending it to us.

The Experiment

Repeated attempts to infect mosquitoes (*Anopheles maculipennis atroparvus*) were made, but results were poor until the last trial (on J.W.), when 84% of a batch of approximately 750 became infective, with concentrations of sporozoites in the salivary glands varying from heavy to very light. These mosquitoes were allowed to feed on one of us (W.C.) on December 18, 19, and 22, 1953; many were made to bite more than once on each day by the process of interrupted feeding. Nine days after the first feed Mr. H. R. I. Wolfe excised a wedge-shaped piece of liver (about 1½ inches at the base) from the patient's left lobe.

Sections were prepared, and revealed the presence of pre-erythrocytic schizonts of *P. ovale*. A few hours after the operation the blood of the patient became flooded with ring forms of the parasite. The tissue forms were in two stages, nearly mature and completely mature schizonts. Their morphology more resembles that of the quartan parasite than of *P. vivax*, but further study of material is necessary before a definite conclusion about the affinities of this parasite can be reached.

Acknowledgments.—We are indebted to Dr. A. R. D. Adams for providing the strain and to Sir Gordon Covell and Mr. P. G. Shute for help in maintaining it. We are very particularly appreciative of the generous help of workers in Dr. Martin D. Young's laboratory in Georgia, U.S.A.—and particularly Dr. G. M. Jeffery—for taking the strain and passing it through numerous patients and mosquitoes, for the purpose of supplying us with an infective batch of mosquitoes if our own experiments had failed. We gladly acknowledge also the invaluable assistance rendered by the surgeon, Mr. H. R. I. Wolfe, Mr. R. Molloy, anaesthetist, and Professor A. W. Woodruff, Dr. S. Bell, and other members of the staff of the Hospital for Tropical Diseases, where we were looked after with kindness and efficiency.

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The Invalid Children's Aid Association's John Horniman Home at Worthing, Sussex, will admit from next April children (girls 7–16, boys 7–14) who need holidays, or care in family crises, but are so severely handicapped that they cannot be received in ordinary convalescent homes. It is hoped to provide for such cases as those with spina bifida, poliomyelitis, congenital deformities, haemophilia, muscular dystrophy, cerebral palsy (I.Q. not below 65), fragilitas ossium, and heart disease (congenital or rheumatic if quiescent). Children suffering from mental defect, epilepsy, blindness, or pulmonary tuberculosis cannot be received. The daily programme will be designed to provide the children with as many interests as possible, and will include handicrafts, painting, modelling, and probably a Guide company and Scout troop. Physiotherapy will be available. Holidays may be arranged ordinarily up to eight weeks. Accommodation will also be available for one or two nights for mothers whose presence may help a child to settle happily. Inquiries should be directed to the general secretary of the association, Miss Rattenbury, 4, Palace Gate, London, W.8.