patory method) gave a systolic pressure of 65.2 mm., and (from a smaller number of observations) a diastolic pressure of 41.6 mm. Since average birth weight is approximately 3.5 kg., the calculated pressures from the formula in newborn infants would be 66.5 mm. systolic and 44.6 mm. diastolic. The approximate average pressures in healthy adults of 70 kg. average weight are generally accepted as being 120 systolic and 80 diastolic. These are to be compared with 121.0 mm. and 81.2 mm. by the formula. The formula calls for 130 mm. systolic and 87.2 mm. diastolic at 100 kg. weight, but I have no normal data for comparison at this weight. It should be repeated that the formula postulates an average normal amount of body fat as essential to the correctness of the factors modifying body weight.

Until the normal variation has been determined the practical value of the formula as a standard of normal blood pressure in individual applications is unknown. At present it is offered merely as an expression of a general trend.

3702

Allergy Response to Tuberculosis in Guinea-Pigs Previously Treated with Tuberculin Fractions and Toxin Filtrates.

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The basis of these experiments is a study of the so-called Koch phenomenon elaborated by Krause[1] on allergy in experimental tuberculosis. The early anatomical response of the tissues of a susceptible animal inoculated for the first time with tubercle bacilli differs from that of a reinfection. In the susceptible guinea-pig a well circumscribed nodular tubercle will develop slowly after a week or more, without any of the signs of inflammation. Only later, after 3 or more weeks, does redness appear around the tubercle, associated with changes that are indicative of a progressive lesion. At this stage the animal has become allergic, *i. e.*, it begins to react in a new way because of the changes set up in the body by the tubercle bacilli. The susceptibility of the animal has been altered. If such an animal now receives an intracutaneous inoculation of tubercle bacilli, the response by the tissue is rapid and local inflammation occurs. In-

stead of well localized proliferation, diffuse exudation takes place. The inflammation occurs rapidly and subsides as rapidly, and the nodular tubercle now present retrogresses and may disappear completely. All of these changes are contingent, however, upon moderate dosages of tubercle bacilli.

In the first group of experiments, 5 series of normal guinea pigs, 3 animals in each series, were used. Subcutaneous injections of the different materials were given weekly in increasing doses over a period of 10 weeks, the initial dose ranging from 0.1 to 0.2 cc., and the final dose from 2.0 to 3.5 cc. Four weeks after the last injection, the animals were inoculated intracutaneously with 0.4 mg. of a moderately virulent strain of human tubercle bacilli. One group received tuberculin fractions*; another, tuberculin fractions and toxin filtrates* injected on alternate weeks; a third group received toxin filtrates alone; a fourth, the same toxin filtrate heated for one hour at 75° C.; and the fifth untreated group served as a control.

The local changes at the site of inoculation on a cleanly shaved area on the back of the animal could be observed from day to day. Attention was paid to the anatomical character of the lesion and the regional lymph node involvement. A record of the body weight and general condition of the animal was kept.

The results of these experiments were uniform and quite conclusive. Having previously noted the differences between a primary infection and a reinfection with tubercle bacilli in the normal animal, it was possible to compare these with the sequence of events in animals previously treated with toxic filtrates and tuberculin fractions injected alone or in combination. If allergy and specific resistance to tubercle infection can be developed artificially with such materials, then a subsequent inoculation of tubercle bacilli should be followed by the reactions that are characteristic of reinfection in a previously tuberculized animal. Such was found to be the case in these experiments. Normal guinea pigs thus treated and inoculated into the skin with tubercle bacilli showed a prompt local reaction noticeable within 48 hours, an early development of nodule in an inflammatory zone, and a lesion that came rapidly to a standstill and tended later to retrogress and heal. The regional lymph nodes did not show the rapid and pronounced enlargement peculiar to untreated control animals. In this instance, early localization and focal involvement

* Alcohol-insoluble fraction and ether-insoluble fraction prepared from culture of moderately virulent human tubercle bacilli grown in synthetic non-protein media. Toxin filtrate (Berkfeld) from 16 to 21 day old cultures of moderately virulent human tubercle bacilli grown in broth. 1 cc. of alcohol-insoluble fraction = 114 mg. tuberculin.

were accomplished in exactly the same manner as that caused by a previous inoculation with tubercle bacilli. However, when guinea pigs had been previously injected with inactivated toxin filtrate, the animals behaved like untreated controls. In these the immediate reaction was uniformly absent; the nodule developed on an uninflamed background in 1 to 2 weeks. The lesion after this time advanced rapidly and approximated the condition seen in reinfected tuberculous animals at the time of reinoculation, and there was a later tendency to progression with softening and caseation.

The most striking and characteristic picture was observed in the groups of animals that received tuberculin fractions alone and in those receiving toxin filtrate and tuberculin fractions in combination. The sharp response appears to be due to the specific bacillary element contained in the tuberculin fraction.

In the second group of experiments, 2 series of normal guinea pigs, including 4 animals in each group, were studied to determine the possible relation between the number of injections and the development of allergy. One set of animals received 2 subcutaneous injections of tuberculin fractions and the other received 4 at weekly intervals. Each group was controlled with an untreated series. In these experiments the results were identical with those previously described. The allergy was developed to a greater degree in those animals receiving the larger number of injections.

The application of Krause's technic in this and similar studies appears to be of definite value, particularly because the mechanism of resistance or immunity can be studied accurately without basing conclusions on dubious differences in viability of the infected experimental animal.

In all respects, regarding the local, regional and constitutional reactions as seen in the different groups of animals, the results justified the conclusion that the allergy phenomena were correlated with the development of specific resistance or immunity. Histopathologic studies confirmed the clinical findings. Two animals in each group were sacrificed 3 months after the inoculation with tubercle bacilli and sections of the lung, liver, spleen and lymph nodes were studied microscopically. The type of reaction seen in the tissues varied with the number of infecting bacilli and confirmed Baumgarten's[2] observations regarding the proliferation of only one type of cell in response to inoculation with few organisms. The structure of the tubercle invariably showed features of a tumor, and had none of the characteristics of inflammation. Although no attempt was made to produce absolute protection against the infecting organism, the observations indicate that definite resistance to the infection must

have been developed, thus substantiating the grossly visible changes at the site of inoculation.

[1] Krause, A. K., *Am. Rev. Tub.*, 1917, i, 65.

[2] Baumgarten, P., Ueber Tuberkel and Tuberkulose. 1. Theil. Die Histogenese des tuberkulösen Processes. Berlin, A. Hirschwold, 1885, (cited by Krause).

3703

Gonad-Stimulating Hormone of Anterior Pituitary and Heterosexual Ovarian Grafts.*

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The rôle of the gonadal-stimulating hormone of the anterior pituitary in the development and regulation of the genital system has been previously reported.[1, 2] That the same stimulation of the ovarian follicle can be effected in ovaries which have been grafted into both normal and castrated males is here reported.

A series of 4 male rats, 96 days of age, may be taken as a typical group. Two of these were castrated and the ovaries of 20-day-old rats were transplanted into the *recti abdomines* and anchored with silk sutures. Into the other 2 unoperated males, ovaries of 20-day-old rats were transplanted, one ovary into each testis. Eight daily transplants of the fresh pituitary of an adult rat were then given to one of the castrated and one of the normal hosts. The other pair received no transplants. The rats were autopsied on the ninth day of the experiment and the grafts removed and sectioned. The ovarian grafts in the recti muscles of the castrated animals were well vascularized, but considerable degeneration, evidently due to an inadequate circulation, had occurred in the untreated animal. In the graft of the animal which had received the pituitary transplants many primary follicles had disappeared, but a score of large follicles, of mature condition and with apparently normal ova, were found.

In the untreated animal of the second pair of this series, the transplanted ovary had been resorbed. In the treated animal there was a typical bilateral ovariotestis. The vascularization was unusually good, and the follicles, both primary and secondary, were numerous. Many large, apparently normal follicles in the graft were

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